USP/NF

Change Process

Pharmacopeial Forum

Topics - New Monograph

- Revised Monograph

- General Chapters

USP/NF

Change Process

Compendial Operations Staff

- **Monitor USP Proposals**
- **Information Conduit**
- **Responsible for Official Comment**
- **Formal Contact with USP**

Question-based Review: Implementing Quality by Design

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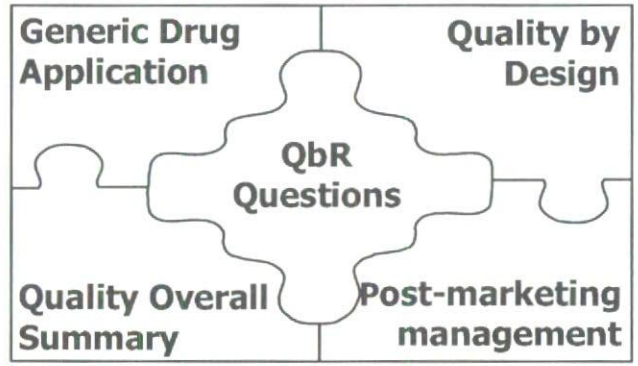
Opinions expressed in this presentation are those of the speakers and do not necessarily reflect the views or policies of the FDA

QbR is a System



Pharmaceutical Quality

$= f$ (Drug Substance, Excipients, Manufacturing, and Packaging)

Janet Woodcock on QbD

J. Woodcock. *Am. Pharm. Rev.*, 2004

- *Quality by Design* "means that product and process performance characteristics are scientifically designed to meet specific objectives... To achieve QbD objectives, product and process characteristics important to desired performance must be derived from a combination of prior knowledge and experimental assessment during product development."

ICH Q8 Describes Quality by Design

- Introduced in ICH Q8
  - "*quality* cannot be tested into products, i.e., quality should be built in by design"
- Product Development Report explains
  - how drug substance properties and formulation variables affect the performance of the drug product
  - how the sponsor identifies the critical manufacturing steps, determines operating parameters, selects in-process tests to control the process, and scales up the manufacturing process

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ISPE PQLI on QbD, Sept. 14, 2007

- Quality by Design is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management. This approach entails the following aspects:
  - Defining the desired product performance, or more generally the Pharmaceutical Target Product Profile
  - Identifying those product characteristics that are Critical Quality Attributes (CQAs)
  - Identifying process parameters and material attributes that can affect CQAs
  - Creating or using an established Knowledge Space to establish one or more Design Space(s) and an appropriate Control Strategy that reliably deliver a product that meets requirements
  - Incorporating the approach into the business plan, product development plan, and assuring and enabling it through the Quality System to facilitate continual improvement throughout the product lifecycle

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What is Quality by Design?

- Quality by Design means
  - designing and developing formulations and manufacturing processes to ensure a predefined quality
- Quality by Design requires
  - understanding how formulation and manufacturing process variables influence product quality
- Quality by Design ensures
  - *Product quality (along with ICH Q9 and Q10)*

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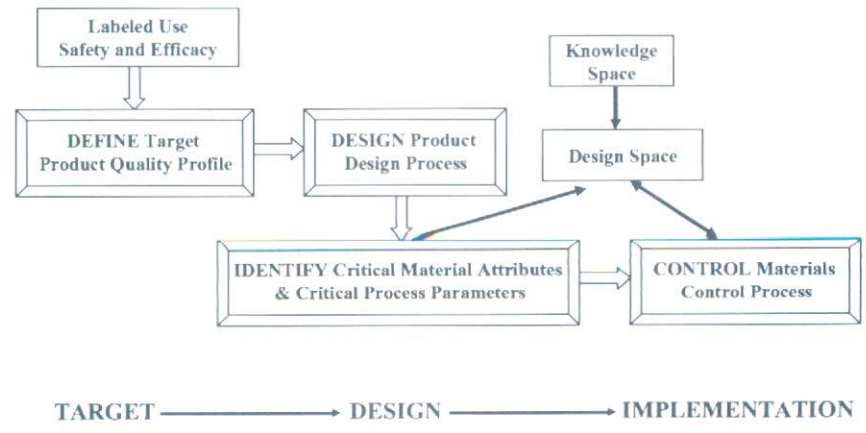
Overview of QbD



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QbD to an FDA Generic Drug Reviewer

- Defining target product quality profile
  - The performance needed to get clinical benefit and meet consumer expectation
- Designing product and processes to meet target product quality profile
- Identifying critical material attributes, process parameters, and sources of variability
  - Design space
- Controlling materials and manufacturing processes to produce consistent quality over time

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Target Product Quality Profile: Beginning the Drug Development with the End in Mind

- FDA's recent guidance on Target Product Profile (TPP)
- The Target Product Quality Profile (TPQP) is a quantitative surrogate for aspects of clinical safety and efficacy that can be used to design and optimize a formulation and manufacturing process
- ISPE PQLI: Pharmaceutical Target Product Profile
- TPQP: Example
  - Assay (uniformity)
  - Purity
  - Stability
  - Desired pharmacokinetic profile
    - In vitro dissolution
    - Bioequivalence

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Designing Product and Processes to Meet Target Product Quality Profile

- Product Design
  - Physical, chemical, and biological properties of drug substance
  - Biopharmaceutics Classification System (BCS) and formulation development
- Process Design
  - Mechanical properties, flow properties, and others
  - Unit operation selection
  - Identification of process parameters and material attributes

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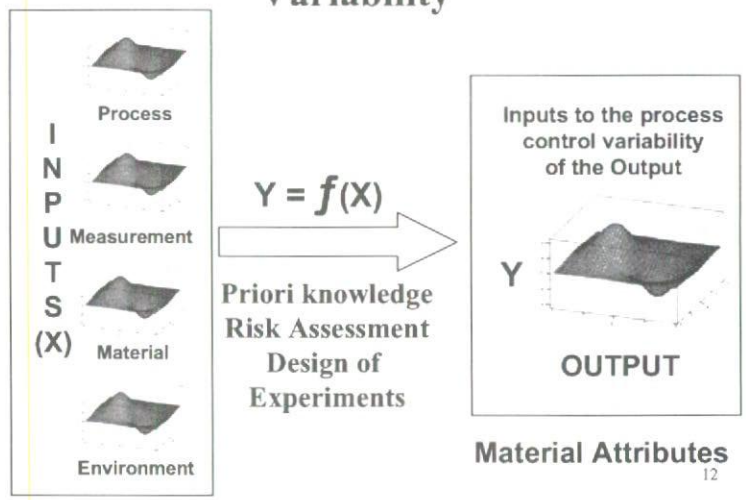
Identifying Critical Material Attributes, Process Parameters, and Sources of Variability



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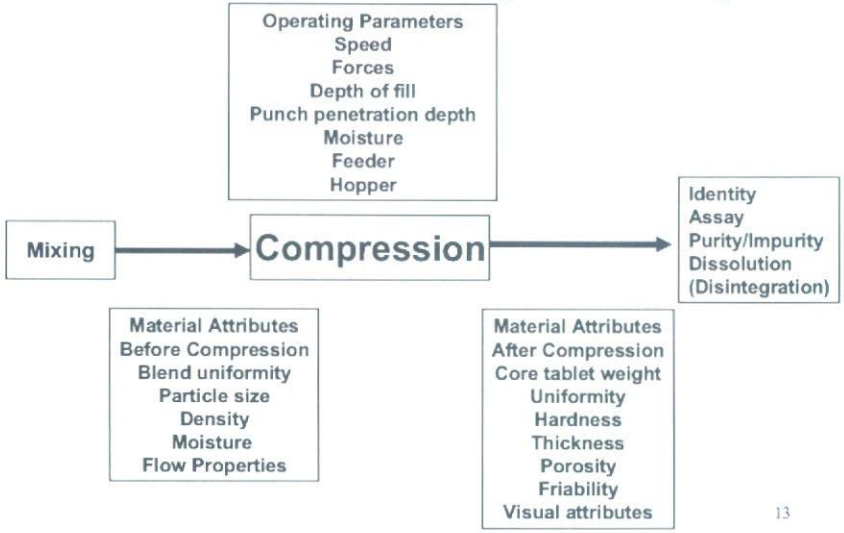
Process Understanding: An Example



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Critical Quality Attribute?

- "A critical quality attribute is a physical, chemical, biological or microbiological property or characteristic that needs to be controlled (directly or indirectly) to ensure product quality."
- "An attribute is a quality or characteristic inherent in or ascribed to something. It may be measurable properties of a material, or *measurable characteristics of the process* to make the material."

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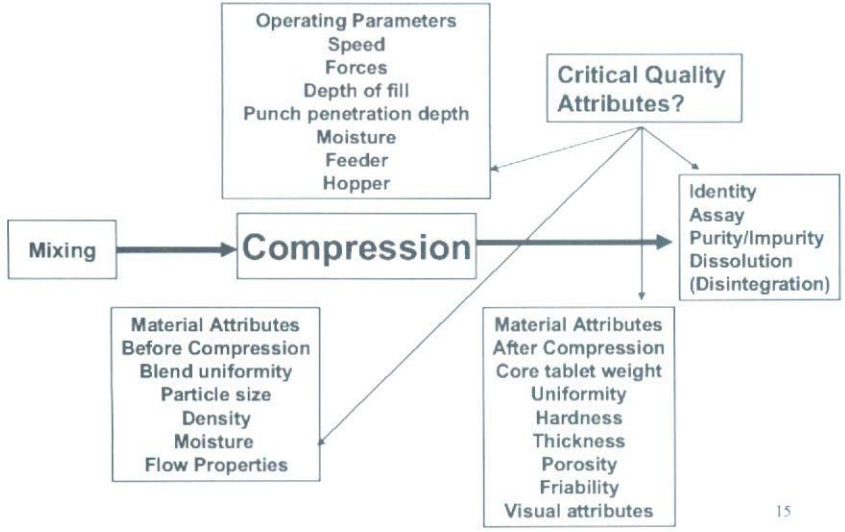
Process Understanding: An Example



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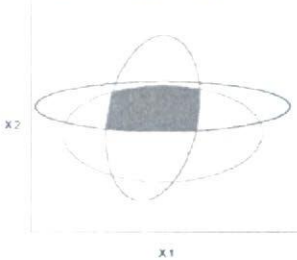
Design Space

- Design Space
  - The **multidimensional** combination and interaction of input variables (eg. Material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process.
- Design space is often established based on *in vitro* "predictive" dissolution



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OGD on Design Space: A Proposal

- Ranges for input materials and process parameters if there are no interactions among them
- Design space can be proposed at the ANDA filing approval
  - Priori knowledge,
  - Risk Assessment, and/or
  - Design of Experiments
- The proposed design space is subject to post approval confirmation
  - Annual Report

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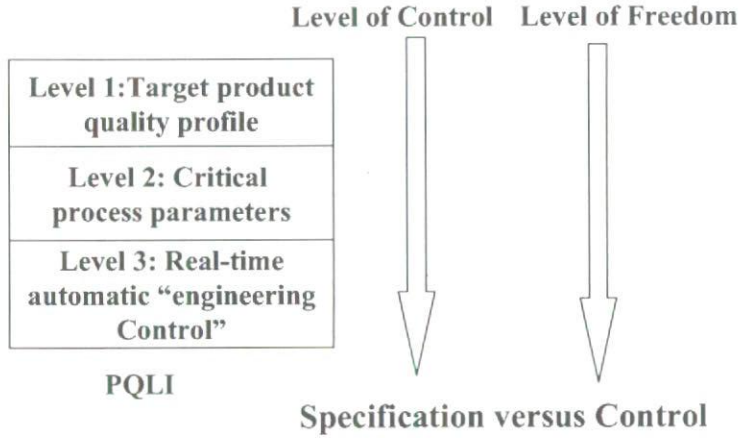
Controlling Input Materials and Manufacturing Processes to Produce Consistent Quality over Time



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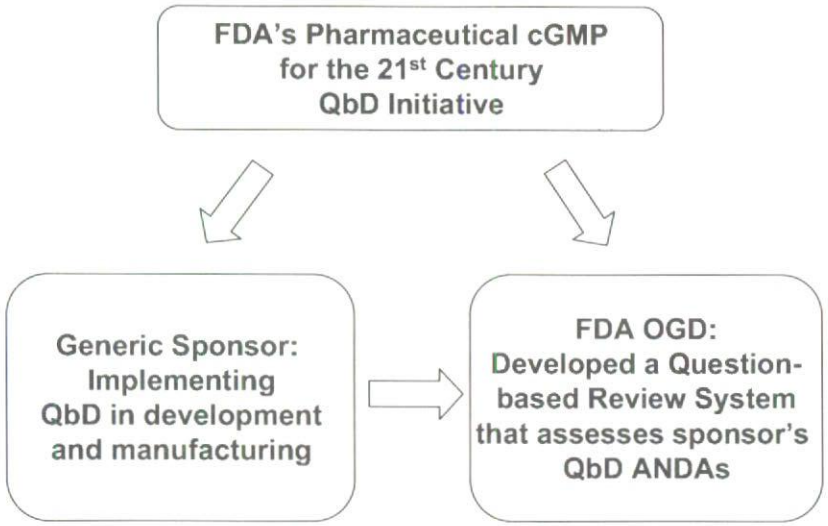

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QbR Questions Provides a Roadmap

- Questions guide reviewers
  - Prepare a consistent and comprehensive evaluation of the ANDA
  - Assess critical formulation & manufacturing variables
- Questions guide industry
  - Recognize issues OGD generally considers critical
  - Direct industry toward QbD
- Questions inform readers of the review
  - How QbD was used in the ANDA
  - Provide the basis for a risk assessment

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How Does QbR Implement QbD? Product Performance

What attributes should the drug product possess?
Answer: What was the goal?

What does OGD mean by attributes in this question?
Answer: Target product quality profile such as assay, purity, dissolution, stability etc.

Continuous Improvement

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How Does QbR Implement QbD? Product Design

How was the product designed to have these attributes?

Were alternative formulations or mechanisms investigated?

How were the excipients selected?

How was the final formulation optimized?

Continuous Improvement

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How Does QbR Implement QbD? Process Design

What are the unit operations in the drug product manufacturing process?

Why was the manufacturing process selected?

How are the unit operations related to the drug product quality?

Continuous Improvement

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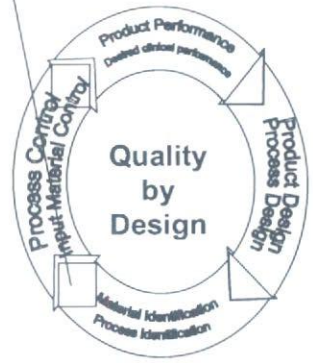
How Does QbR Implement QbD? Material and Process Identification

Which properties or physical chemical characteristics of the drug substance affect drug product development, manufacture, or performance?

What evidence supports compatibility between the excipients and the drug substance?

How were the critical process parameters identified, monitored, and controlled?



Continuous Improvement

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Critical Material Attribute and Process Parameter

- A Critical Material Attribute is a physical, chemical, biological or microbiological property or characteristic of a material that needs to be controlled (directly or indirectly) to ensure product quality.
- A Critical Process Parameter is a process parameter whose variability impacts a quality (material) attribute and therefore needs to be controlled to ensure the process produces the desired quality. A critical process parameter remains critical even if it is controlled.

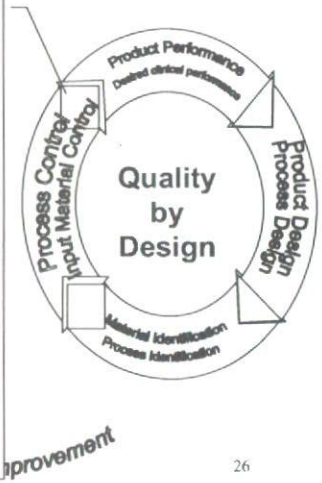
How Does QbR Implement QbD? Process and Input Material Controls

What are the in-process tests and/or controls that ensure each step is successful?

What is the scale-up experience with the unit operations in this process?

In the proposed scale up plan what operating parameters will be adjusted to ensure the product meets all in-process controls and final product specifications?

What evidence supports the plan to scale up the process to commercial scale?



QbR Communications

- **www.fda.gov/cder/ogd/QbR.htm**
  - **QbR White Paper**
  - **QbR Questions**
  - **QbR Frequently Asked Questions**
  - **QbR mock examples**
  - **QbR updates**
- **Publications on QbR**
  - ***J. Generic Medicine, Pharm. Eng….***
- **Workshops, Webcast, and Teleconf.**

Conclusion

- **The FDA OGD has developed a Question-based Review for quality assessment. It is a concrete and practical implementation of the underlying concepts and principles outlined by the FDA's Pharmaceutical CGMPs for the 21st Century and Quality by Design (QbD) initiatives**

Questions to be completed by ANDA Sponsors for the preparation of a QbR-Quality Overall Summary

Pharmaceutical Product Quality: Question-based Review for ANDAs

Definition: Simple Dosage Form - Either a solution or an IR solid oral dosage form

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product

Non-Proprietary Name of Drug Product

Non-Proprietary Name of Drug Substance

Company Name

Dosage Form

Strength(s)

Route of Administration

Proposed Indication(s)

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

2.3.S.2 Manufacture

Who manufactures the drug substance?

How do the manufacturing processes and controls ensure consistent production of drug substance?

2.3.S.3 Characterization

How was the drug substance structure elucidated and characterized?

How were potential impurities identified and characterized?

2.3.S.4 Control of Drug Substance

What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?

For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

2.3.S.5 Reference Standards

How were the primary reference standards certified?

2.3.S.6 Container Closure System

What container closure system is used for packaging and storage of the drug substance?

2.3.S.7 Stability

What drug substance stability studies support the retest or expiration date and storage conditions for the drug substance?

2.3.P DRUG PRODUCT

2.3.P.1 Description and Composition

What are the components and composition of the final product? What is the function(s) of each excipient?

Does any excipient exceed the IIG limit for this route of administration?

Do the differences between this formulation and the RLD present potential concerns with respect to therapeutic equivalence?

2.3.P.2 Pharmaceutical Development

2.3.P.2.1 Components of the Product

2.3.P.2.1.1 Drug Substance

Which properties or physical chemical characteristics of the drug substance affect drug product development, manufacture, or performance?

2.3.P.2.1.2 Excipients

What evidence supports compatibility between the excipients and the drug substance?

2.3.P.2.2 Drug Product

What attributes should the drug product possess?

How was the drug product designed to have these attributes?

Were alternative formulations or mechanisms investigated?

How were the excipients and their grades selected?

How was the final formulation optimized?

2.3.P.2.3 Manufacturing Process Development

(If the Product is a NTI Drug or a Non-Simple Dosage Form)

Why was the manufacturing process described in 2.3.P.3 selected for this drug product?

How are the manufacturing steps (unit operations) related to the drug product quality?

How were the critical process parameters identified, monitored, and/or controlled?

What is the scale-up experience with the unit operations in this process?

2.3.P.2.4 Container Closure System

What specific container closure attributes are necessary to ensure product performance?

2.3.P.3 Manufacture

(For All Products)

Who manufactures the drug product?

What are the unit operations in the drug product manufacturing process?

What is the reconciliation of the exhibit batch?

Does the batch formula accurately reflect the drug product composition? If not, what are the differences and the justifications?

What are the in-process tests and controls that ensure each step is successful?

(If Product is Not a Solution)

What is the difference in size between commercial scale and exhibit batch? Does the equipment use the same design and operating principles?

(If the Product is a NTI Drug or a Non-Simple Dosage Form)

In the proposed scale-up plan what operating parameters will be adjusted to ensure the product meets all in-process and final product specifications?

What evidence supports the plan to scale up the process to commercial scale?

2.3.P.4 Control of Excipients

What are the specifications for the inactive ingredients and are they suitable for their intended function?

2.3.P.5 Control of Drug Product

What is the drug product specification? Does it include all the critical drug product attributes?

For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

2.3.P.6 Reference Standards and Materials

How were the primary reference standards certified?

2.3.P.7 Container Closure System

What container closure system(s) is proposed for packaging and storage of the drug product?

Has the container closure system been qualified as safe for use with this dosage form?

2.3.P.8 Stability

What are the specifications for stability studies, including justification of acceptance criteria that differ from the drug product release specification?

What drug product stability studies support the proposed shelf life and storage conditions?

What is the post-approval stability protocol?

Quality by Design Case Studies – the FDA CMC Pilot Program

Chi-wan Chen, Ph.D.
Office of New Drug Quality Assessment (ONDQA)
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration (FDA)

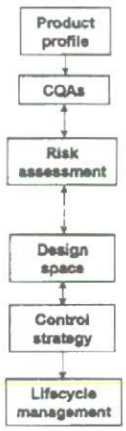
FIP Workshop on
Quality by Design and Quality Risk Management
Beijing, China
August 31, 2007

Outline

- CMC Pilot objectives and status
- QbD – a system approach
- Case studies
  - #1: Risk assessment and design space
  - #2: Real time release
  - #3: Drug substance CQAs
  - #4: Drug substance CQAs
- Summary of CMC Pilot
  - Risk assessment
  - Design space
  - Control strategy
  - Overall
- Next steps

2

QbD – a Systematic Approach



- 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

3

CMC Pilot Objectives and Status

- Objectives
  - To provide participating firms an opportunity to submit CMC information demonstrating application of QbD
  - To enable FDA to evaluate utility of CQOS and to implement new concepts (e.g., QbD, design space, real-time release) in Q8, Q9, and PAT Guidance
- Status
  - Program launched July 2005
  - 9 original and 2 supplemental NDAs accepted
  - 7 submitted to date: 5 approved, 1 approvable, 1 under review (as of June 11, 2007)
  - Others to be submitted within a year

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Case Studies

The following case studies are based on select CMC Pilot NDAs and are presented with permission from the applicants

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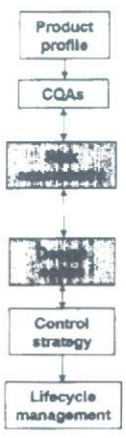
Case Study #1



Risk Assessment and Design Space

6

Product X

- Target product performance
  - Extended release formulation required for once-a-day dosing
    - Relatively high dose compound
    - High water solubility, moderate permeability
- Formulation
  - Controlled release using a polymer
  - Level-A IVIVC established

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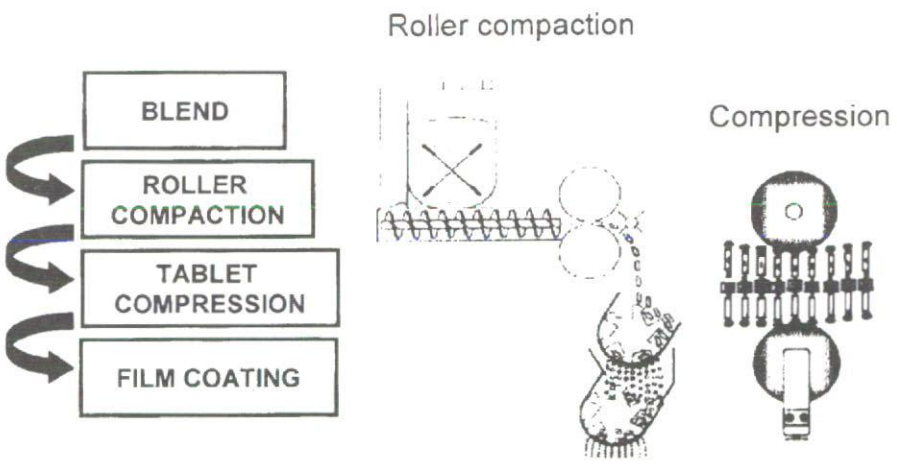
Manufacturing Process



Applying QbD

- Establish product critical quality attributes (CQAs)
  - Dissolution
  - Tablet hardness
- Link material attributes and process parameters to CQA
- Perform quality risk assessment
- Establish a design space
- Establish sound control strategy to ensure consistent product quality and performance

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Quality Risk Assessment

Failure Mode and Effect Analysis (FMEA)

Select process parameter / Quality Attribute	Polymer Concentration	API Particle Size	Roll Gap	PSD of Intra-granular Blend	Compressing Force	Weighted Average
Dissolution	10	1	1	1	1	10
Assay	3	5	7	1	1	9
Uniformity	1	5	7	4	1	7
Hardness	5	5	10	4	10	10
Yield	1	1	3	3	1	7
Rank	1	7	2	8	5	

Risk Prioritization

- Rating
  - Probability
  - Severity
  - Detectability
- Semi-quantitative values assigned using knowledge management
  - Multidisciplinary expert teams
  - Prior knowledge
  - Development experiments

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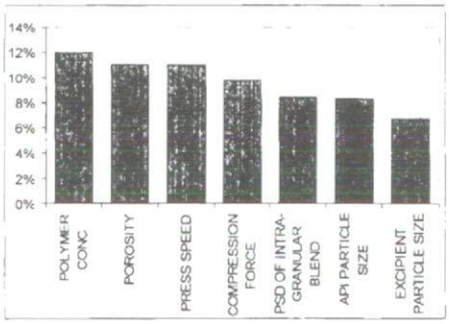
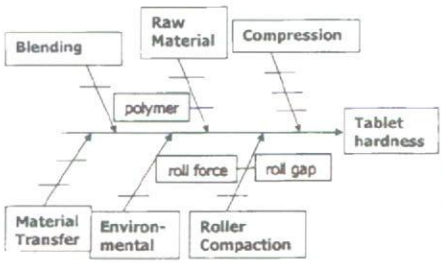
Risk Analysis to Identify CQA, CPP

Pareto Analysis



Relative importance of inputs based on FMEA

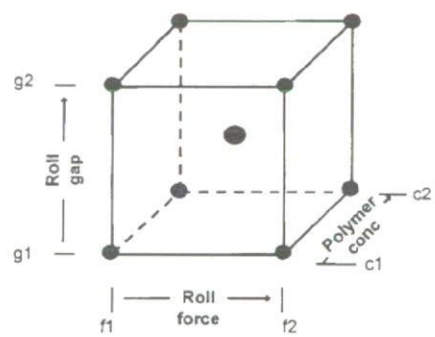
Ishikawa Diagram for Tablet Hardness



Identify critical input/process variables

Establishing Design Space

Design of Experiments (DOE)



DOE: Efficient method to evaluate the impact of input variables and process parameters (on product CQAs) and their interactions (not just correlations)

Critical input variables/process parameter:

- Polymer concentration
- Roll gap
- Roll force

Intermediate attributes:

- Porosity
- Compressibility

CQAs:

- Dissolution
- Hardness

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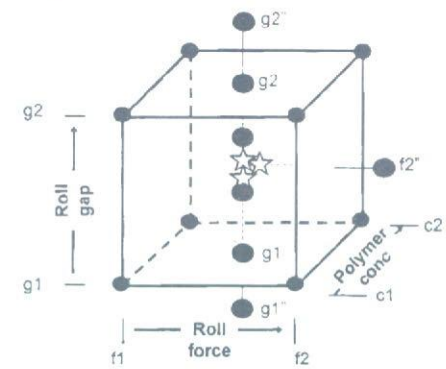
Confirming Design Space



- Design space for roller compaction predicted based on pilot scale is confirmed with production scale batches
- Production scale batches outside the design space failed tablet compression

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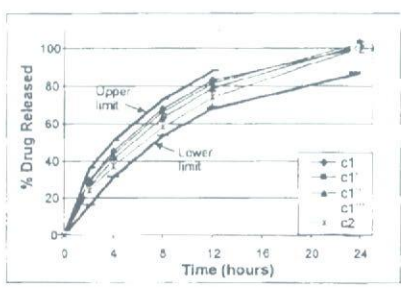
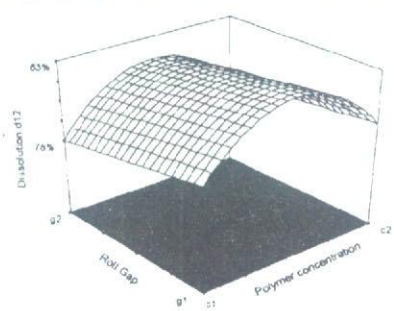
Establishing Design Space (cont'd)

Effect of Polymer Concentration on Dissolution



Typical 2-dimensional analysis

Interaction Effect of Roll Gap and Polymer Concentration on Dissolution



Z: Dissolution – d12
X: Polymer concentration
Y: Roll gap
Roll force fixed at f bar

Impact of Polymer Attributes on Performance – DOE Results

- Dissolution rate is dependent on polymer concentration
- Dissolution rate is largely independent (in the ranges studied) of
  - Roll force, roll gap, compression force
  - Polymer viscosity, particle size, substitutions
  - API particle size distribution
  - Tablet hardness
- Formulation performance is robust and resistant to variability in excipient and API inputs
- Design space established for polymer, API, compaction, compression

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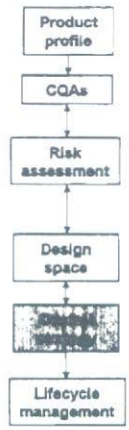
QbD vs. Traditional Approach – a simplified comparison

Aspect	Product X With QbD	Traditional
Product Quality Attributes	▪ Dissolution ▪ Tablet hardness	▪ Dissolution
Excipients	▪ Effect of polymer physical and chemical attributes understood ▪ Design space established	▪ Effect of polymer attributes unknown ▪ Reliance on USP spec
Manufacturing Process	▪ Process understood ▪ Design space established ▪ Process robust and adjustable	▪ Process not understood ▪ Operating ranges based on validation, focusing on repeatability ▪ Process changes at risk and fixed
Control Strategy	▪ Comprehensive, inc. control of input and process variability ▪ Predictive	▪ Limited, relying on end-product testing ▪ Reactive

Case Study #2



Control Strategy – Real Time Release

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Product Y

- Target product performance
  - Immediate release tablet
  - High water solubility, moderate permeability
- Formulation
  - Simple formulation
  - Common blend for all strengths

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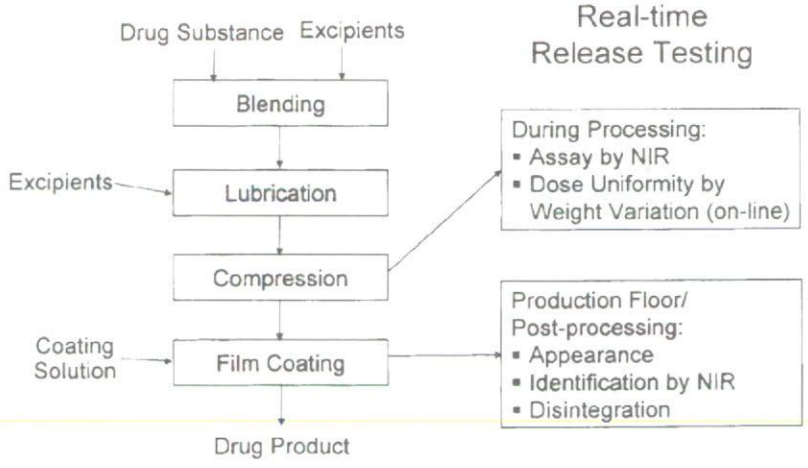
Drug Product Manufacturing



Traditional Release Testing

- Laboratory testing performed on samples after processing is complete
- Limited sampling
  - Very few samples taken
  - Samples may not adequately represent entire batch
- No opportunities to fix problems
  - Pass/Fail decisions only
  - Little information for fault diagnosis

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