ISPE, Yokohama, Japan
June 9, 2006

Implementation of ICH Q8 and QbD – An FDA Perspective

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Outline

- ICH Q8
- FDA's implementation of Q8
- FDA's view on quality by design (QbD)
- QbD system for pharmaceutical development
- FDA CMC (chemistry, manufacturing, & controls) Pilot Program
- Summary

Q8 - 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
- 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 post-approval change process.
- Design space is proposed by the applicant and is subject to regulatory assessment and approval

Q8 - Regulatory Flexibility

- Proposed by applicant, and approved by regulator, based on demonstrated product knowledge and process understanding
- Degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided
- Opportunities to facilitate
  - risk-based regulatory decisions (reviews and inspections)
  - manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review
  - reduction of post-approval submissions
  - real-time quality control, leading to a reduction of end-product release testing

FDA's Implementation of Q8

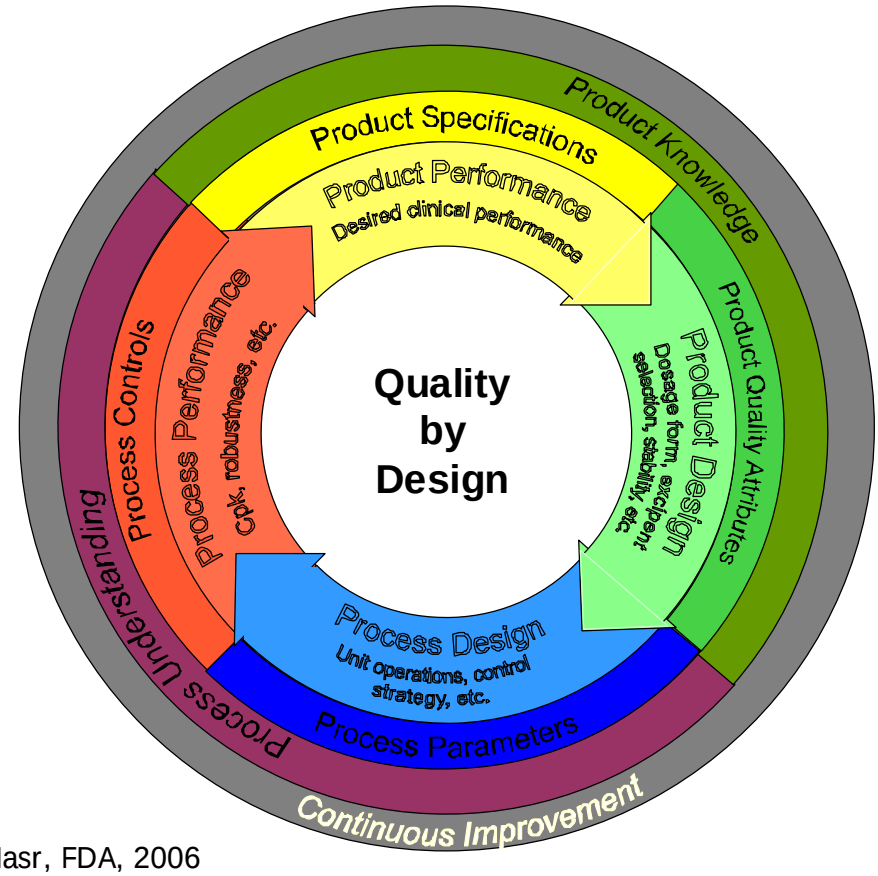
- Reorganization of Office of New Drug Chemistry to become Office of New Drug Quality Assessment (ONDQA) in November 2005
  - Separation of pre-marketing from post-marketing review activities to better utilize limited resources
  - Establishment of Manufacturing Science Branch and recruitment of pharmaceutical scientists, chemical engineers, and industrial pharmacists to complement current review staff
- Establishment of a new pharmaceutical quality assessment system (PQAS)
- Public workshops (10/05 & 2/07) on quality-by-design
- CMC Pilot Program

Pharmaceutical Quality Assessment System

- PQAS is ONDQA's new science- and risk-based approach to CMC review that
  - Emphasizes submissions rich in scientific information demonstrating product knowledge and process understanding
  - Focuses on critical pharmaceutical quality attributes and their relevance to safety and effectiveness
  - Enables FDA to provide regulatory flexibility for specification setting and post-approval changes
  - Facilitates innovation and continuous improvement throughout product lifecycle

FDA's view on Quality by Design (QbD)

- In a Quality-by-Design system:
  - The product is designed to meet patient requirements
  - The process is designed to consistently meet product critical quality attributes
  - The impact of starting materials and process parameters on product quality is understood
  - Critical sources of process variability are identified and controlled
  - The process is continually monitored and updated to assure consistent quality over time



Moheb Nasr, FDA, 2006

FDA's View on QbD

- The CMC information currently required in an NDA is adequate to support approval in the U.S.
- However, QbD is the desired approach
  - QbD principles should result in a higher level of assurance of product quality
  - Additional product and process understanding may result in regulatory flexibility
- QbD is full understanding of product and process as they relate to product performance
  - QbD is more than process and formulation optimization
  - QbD is more than justification of CQAs and CPPs
  - This may be an iterative/continuous process

QbD System – Product Performance and Product Design

- Define targeted product performance requirements in early phases of development
  - route of administration, dosage form, strength, optimum dose, therapeutic index, PK profile, etc.
- Product Design
  - Identify critical quality attributes of DP to meet targeted product performance requirements
  - Formulation components
    - Select excipients based on compatibility and product performance requirements
    - Understand chemical and physical properties of DS and excipients and how they may influence downstream manufacturability, process parameters, and/or product performance
    - Understand variability of components and how to best control it

QbD System – Process Design

- For each unit operation
  - Understand how process parameters affect CQAs
  - Determine critical process parameters and operating ranges
  - Establish appropriate process controls to minimize effects of variability on CQAs

QbD System – Design Space

- Establish design space with supporting data
  - Formulation development information
  - Process development information
  - Risk analysis/assessment and risk mitigation strategies
  - Identification of and justification for critical and non-critical parameters for each unit operation
  - Evaluation of interaction of operations as outputs of each unit operation become inputs for the next operation
  - Use of PAT as a valuable tool

QbD System – Designing/Setting Specifications

- Relate specifications to critical quality attributes
  - Summarize how relationships were established
    - DOE
    - Prior knowledge
- Base specifications on CQAs and product and process understanding
- Propose acceptance criteria based on scientific rationale by using appropriate methods, including statistical analysis

QbD System – Regulatory Flexibility

- Certain traditional end product release testing may prove to be unnecessary (dissolution, content uniformity, etc.) through QbD
- Supportive data are needed to justify an expanded design space that could serve as the basis for future regulatory flexibility (e.g., site change and equipment change)
  - Design space for one type of dryer vs. design space for any kind of drying
- Opportunities for real time release (RTR)

CMC Pilot Program - Objectives

- To provide participating firms an opportunity to submit CMC information demonstrating
  - application of quality-by-design (QbD) principles
  - product knowledge and process understanding
- To enable FDA to evaluate
  - CQOS; new concepts and approaches (e.g., design space, real-time release) in Q8 and PAT Guidance; CMC Agreement; team review
- To enable FDA to seek public input in developing a guidance on the new PQAS

CMC Pilot - Expanded PD (P.2)

- 3.2.S.2.6 in certain pilot NDAs provided more process understanding information in DS than in typical NDAs
- 3.2.P.2 in all pilot NDAs provided more scientific information than typical NDAs regarding DP
  - formulation and product development
  - process understanding and optimization
- All pilot NDAs to date contained some aspects of QbD, though not the entire system approach
- Most demonstrated process reproducibility, but not necessarily process robustness

CMC Pilot - Application of QbD

The following were in various pilot NDAs:

- Critical quality attributes (CQAs) identified
- Impact of excipients properties discussed
- Design space for process parameters established
- Process reproducibility, but not necessarily process robustness, demonstrated
- Process analyzers used to collect data in development, but not for commercial production

CMC Pilot - Design Space

- Issues raised:
  - How were design space and control space established for each unit operation?
  - Is the design space for each unit operation independent of equipment design and batch size?
  - How does control space relate to design space?
  - How does control space relate to operational ranges in the Master Batch Record?

CMC Pilot - Regulatory Flexibility

- Examples of proposed regulatory flexibility:
  - In-process testing in lieu of end-product testing, e.g., blend uniformity in lieu of content uniformity
  - Real-time release in lieu of end-product testing
  - Annual report for post-approval changes within established design space for non-CPPs
  - CBE for changes within established design space for CPPs
- Degree of flexibility granted would depend on level of demonstrated knowledge and understanding

CMC Pilot - Design Space Changes Post-Approval

Issues raised:

- How will the design space be reassessed, verified, or redefined when a change is made in a unit operation, process parameters, in-process controls, or when a new piece of equipment is introduced?
- What is the regulatory strategy for managing changes in design space, including expanding and contracting the design space, for critical and non-critical parameters?

CMC Pilot - Regulatory Agreement

- An agreement between FDA and applicant which
  - Identifies CQAs, CPPs, and design space
  - Describes how changes to CQAs and CPPs will be managed
  - Describes how design space will be reassessed, verified, or redefined
    - when a change is made in a unit operation, process parameters, in-process controls, or
    - when a new piece of equipment is introduced
  - Describes the regulatory strategy for managing changes in design space, including expanding and contracting, for CPPs and non-CPPS

CMC Pilot - Benefits

- Pilot enables industry and FDA to
  - explore ways to implement Q8 and PQAS
- Pilot enables FDA to
  - better define what constitutes a QbD-based submission
  - better define what constitutes a science-based risk assessment
  - use experience gained to develop a guidance on QbD and PQAS
- Good science leads to better quality product, fewer product rejects/recalls, and enhanced public health protection

CMC Pilot - Challenges

- Level of detail in submission demonstrating product knowledge and process understanding
- Expectations for a QbD-based submission while addressing traditional requirements
- Providing regulatory flexibility while assuring product quality
- Industry's continuous apprehension in sharing information, including failed experiments, with FDA
- Cultural changes needed in industry and FDA
- More resources needed initially

Summary

- FDA embraces Q8 and encourages applicants to apply QbD principles to their drug development
- FDA is exploring ways to facilitate implementation of Q8 and QbD
- CMC Pilot Program is very useful to FDA as it implements QbD and develop PQAS
- FDA is committed to developing ICH Q8(R) to provide additional guidance and clarity on PD
- Challenges remain for industry and FDA as we move forward

Pharmaceutical Quality Forum: 5th Symposium, **Yokohama**

June, 2006

Design Space

Japanese Industry's Perspective

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JPMA Q8 deputy topic leader

Takeda Pharmaceutical Company Ltd.

Content of the Presentation

1 Background

2 Discussion on Design Space
- Design Space for manufacturing process
- Design Space for formulation attribute

3 Revised Pharmaceutical Affairs Law

4 Proposal from JPMA

5 Conclusion

Current Status in Japan

1. (Still) Lack of understandings of concepts proposed by Q8, esp. ***Design Space***.
   - "high level" examples provided by Q8R

2. Recently Revised Pharmaceutical Affairs Law and Q8
   - discussion with MHLW for implementation

3. High Quality Product supplied through flexible approach
   e.g. Prospective validation
   "design space"-like approach
   e.g. "Biryo" component, Sufficient amount,
   Primary packaging material

(Notification from Director of Review Management 39、 February 2000；医薬審 第39号 平成12年2月8日)

Current Status in Japan

4. Limited development budget
   ・Less space at submission
   →Less opportunity for flexibility??
   →Categorized as "high risk" by authority??

5. Cost/benefit analysis for post approval changes
   - additional changes of law??
   - Incentives

Design Space

Initial definition in Step 2 document
(Yokohama, November 2004)

- Established range of process parameters that has been demonstrated to provide assurance of quality

- In some cases design space can also be applicable to formulation attributes

Design Space ; Current version

Defined in Step 4 document (Chicago, November 2005)

Design Space: the *multidimensional* combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

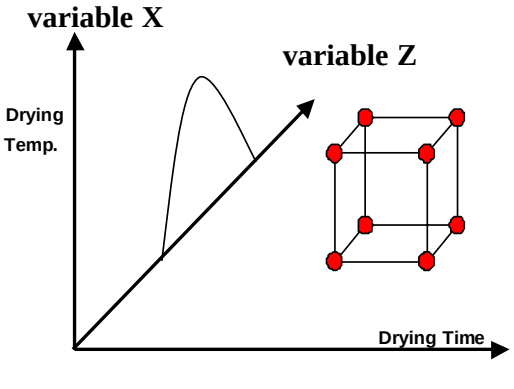
Working within the design space is not considered as a change.

Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Design Space ; Example

Raw Material Attribute
Intermediate Product Attribute
Formulation Attribute



Specification of

raw material

intermediate products

- Design Space with input variables would be complicated.

Desired State (Line 34-55)

→more Flexible regulatory approach (Line 72-76)

Design Space
Quality by Design

In addition, ・・・ (Line 63-88)

expanded design space (Line 68)

formal experimental designs, PAT (Line 81)

Baseline expectations ・・・ (Line 135-309)

Process development studies ・・・process validation ・・・(Line 210-211)

At a minimum, ・・・ (Q8 Step 4, Line 57-61)

Toward the end of Desired State

Knowledge, Process Understanding

Japanese Pharmaceutical Affairs Law

Requirement of detailed description in application form about manufacturing and manufacturing control

Approval matters

Partial change after review

Minor change by notification

Japanese Pharmaceutical Affairs Law

Target Value / Set Value

Permissible range of target value / set value must be described on the master production documents or SOPs.

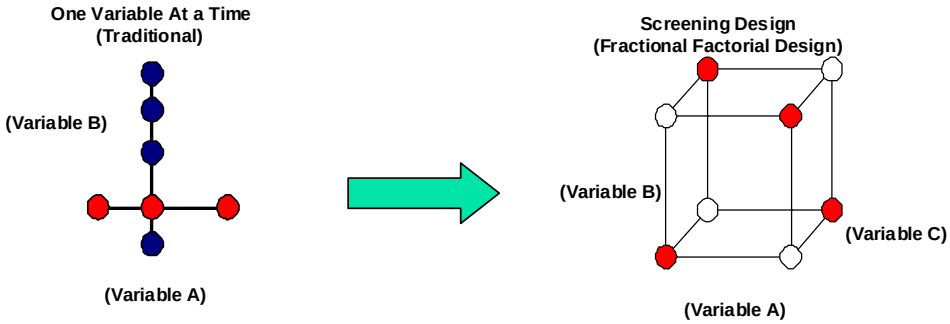
In case of that parameter can affect the quality significantly:

A permissible range should be specified in the format for approval.

Formal Experimental Design

a *structured, organized method* for determining the relationship between factors affecting a process and the output of that process.

Also known as "Design of Experiments".



Traditional

Design of Experiment

Example Manufacturing Parameters

Case Study in Takeda

Run	Factor 1	Factor 2	Factor 3	Factor 4
1	4000(-)	10(+)	80(+)	360(-)
2	4000(-)	10(+)	70(-)	420(+)
3	5000(+)	10(+)	80(+)	420(+)
4	4000(-)	6(-)	70(-)	360(-)
5	5000(+)	10(+)	70(-)	360(-)
6	5000(+)	6(-)	80(+)	360(-)
7	5000(+)	6(-)	70(-)	420(+)
8	4000(-)	6(-)	80(+)	420(+)

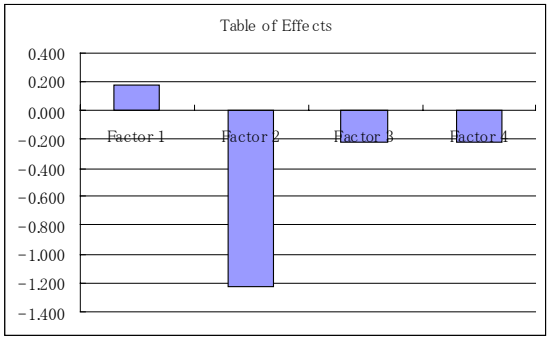
Specification

Content, Content Uniformity, Dissolution etc

Design of Experiment

Example Manufacturing Parameters
Case Study in Takeda

Multivariate Analysis
Determining which parameters drive effects



Met Specification

Content, Content Uniformity, Dissolution etc

Design Space would be

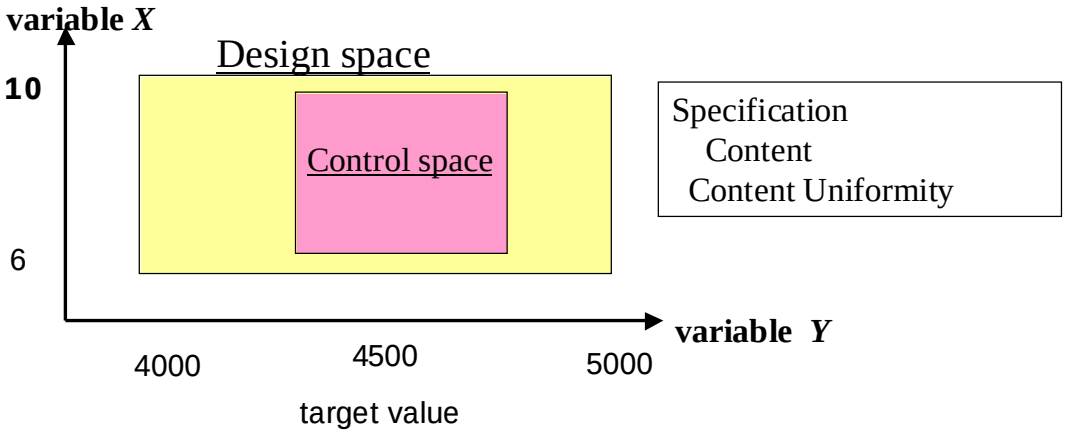
Parameter 1: 4000 - 5000

Parameter 2: 6 - 10

Parameter 3: 70 - 80

Parameter 4: 360 - 420

Design space VS Control space



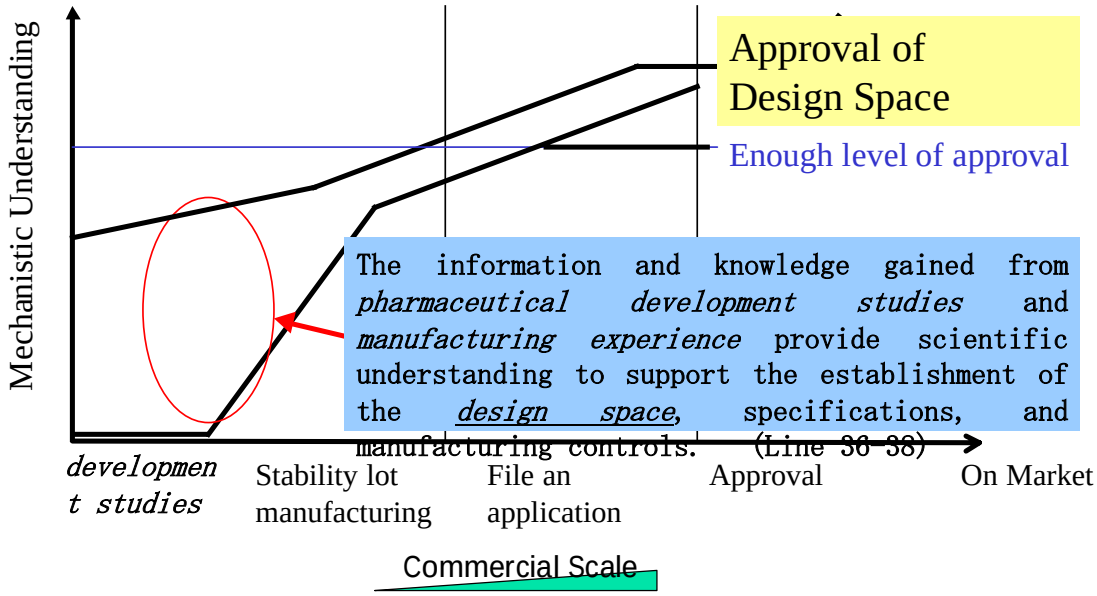
Need to make clear the relation with Design Space and

Target Value / Set Value

Permissible range

in Revised Pharmaceutical Affairs Law

Approval of Design Space; Example



Design Space; （JPMA Proposal）

Advanced ? Traditional Approach vs Enhanced Approach

Advanced ? Traditional Approach and Design Space

Example: For IR tablet through fluid bed granulation

- （Japanese formulator's preference）
- Prior knowledge within a company
- Knowledge learned from manufacturing process for Commercial Products
- Perspective Validation

Enhanced Approach and Design Space

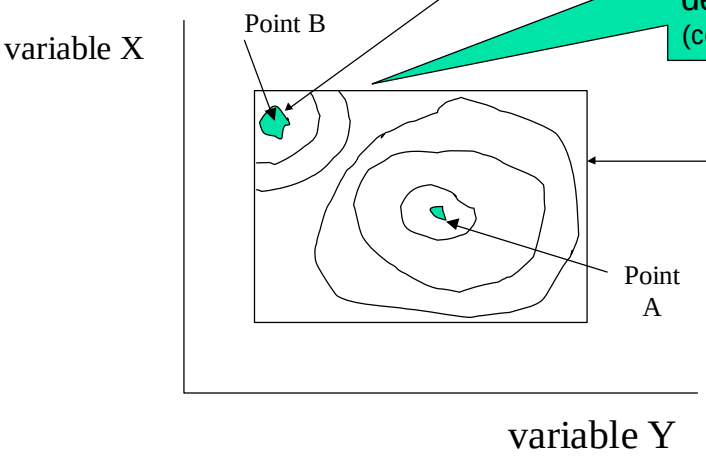
1. formulation development （Formal Experimental Design）
2. DOE for commercial production scale

Discussion on Regulatory Flexibility

ICH Q8 London meeting (March 2004)

Traditional process – limited knowledge – 3 batches, any change needs new data and new approval

Knowledge learned during development stage was not well described in an dossier. (comment from JPMA)



New paradigm:

- influence of factors explored creating knowledge.
- Risk analysis of impact of change possible.
- Approval to move within defined area post-approval could give flexibility for continuous improvement without need for further approval

Previous Process Study

Results of study for industrialization

Past production records of similar products

Identification

Variation factors

- Physical properties of raw materials
- Operating conditions

etc

Quality of products

Prospective Validation

Permissible manufacturing conditions

Upper limit of the permissible manufacturing conditions

Constant manufacture of drugs of intended quality

Lower limit of the permissible manufacturing conditions

Verification of suitability

薬食監麻発330001号
Validation Standards

Definition of Prospective Validation

Acknowledgments: Tadatsugu Tanino, Ph. D. Shionogi & Co. Ltd.
(Slide is revised for English referred with "The Japanese GMP Regulations 1998, YAKUJI NIPPO, LTD.)

JPMA Proposal

	Development Stage	manufacturing parameters for commertial scale		Comment
Previous Style for Application	Knowledge was not well described in the Application, although applicants understand or it was not required	Validation 3Lots	(Design Point)	No Good
Baseline (Q8 step 4)	Knowledge	(Design Space)	Vaildation 3Lots	Acceptable
Quality by Design ~~Desired State~~	Knowledge	Design Space	continuous process verification	Desired State (Excellent companies)

- More flexible opportunities for both process and formulation
- Validation approach with Knowledge as a base for Design Space

Design Space for Formulation Attributes

Formulation	A	B	C
Active Substance	10	10	10
Excipient 1	0.1	0.2	0.3
Others	89.9	89.8	89.7
Total (%)	100	100	100

Formulation	A	B
Active Substance	10	10
Excipient 1	80	0
Excipient 2	0	80
Others	10	10
Total (%)	100	100

Design Space for Formulation Attributes

- **Sufficient amount**

Phenobarbital Powder
10% Phenobarbital Powder

Method of preparation

Phenobarbital	100 g
Starch, lactose or their mixture	a sufficient quantity
	To make 1000 g

- **"Biryo"** : less than 0.1% of total amount

e.g. flavor, coloring agent

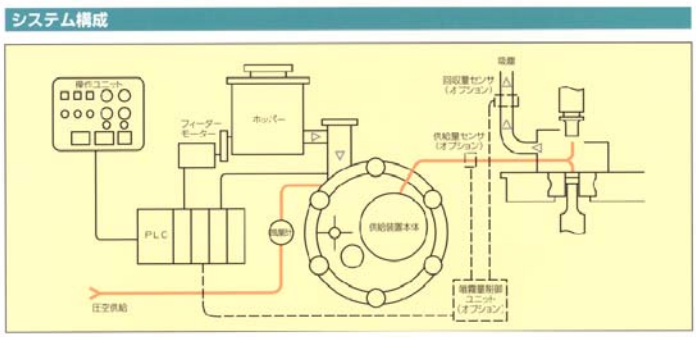
Except: stabilization agent, antioxidants, preservatives

Design Space for Formulation Attributes
Examples of Lubricant

Extra Lubricating System: By applying small amount of lubricant to the punch and die surface just before compression, to avoid problems (such as sticking)

（Merit） Decrease of lubricant amount compared to conventional method

Tablet hardness ↑ Tablet disintegrating time ↓



Design Space for Formulation Attributes
Examples of Lubricant

The amount of lubricant in each tablet is variable.

（Example 1） less than 0.1 %

→ Not regarded as “Biryo”

（Example 2） 0.21~ 1.16 %

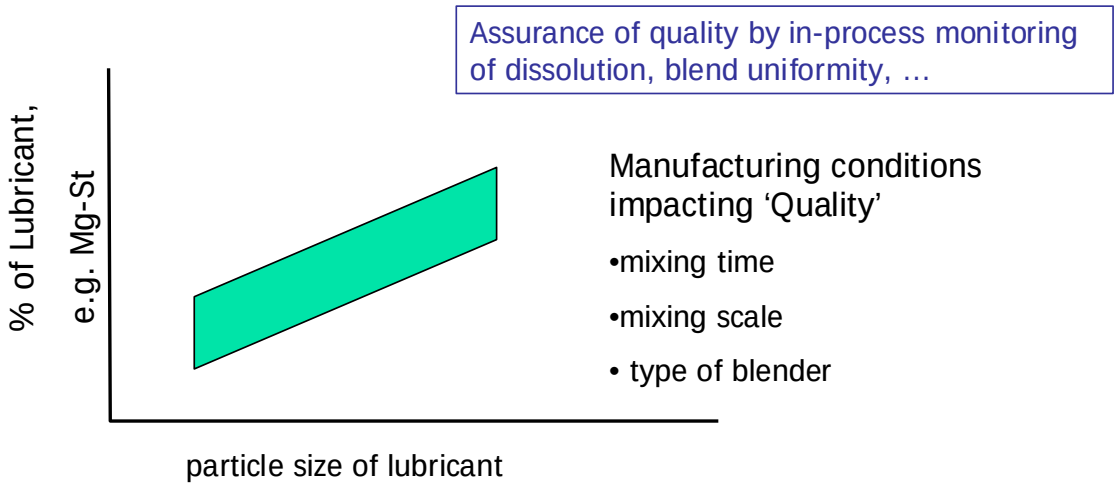
Opportunities for More Flexible approach !

Applicants need to discuss with authorities to establish the design space.

IPJ-2 (INTERPHEX JAPAN May 17 2006)

Formulation attributes are described in the case of Design Space by National Institute of Health Sciences.

Design Space for Formulation Attributes
Examples of Lubricant



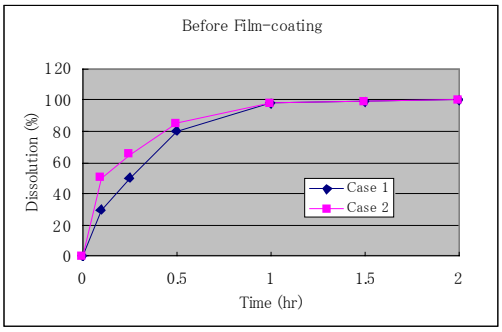
Design Space for Formulation Attributes
Examples of coating material

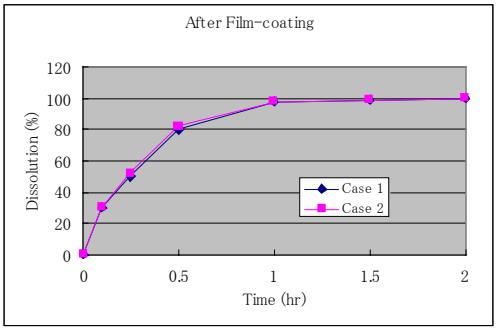
Adjust the formulation by monitoring the intermediate product quality

Example **Design Space 6-12mg for the amount of film-coating**

Adjust the film-coat amount based on the dissolution profile of intermediates

Case 1 10mg Case 2 8mg





Future Activities

- **ICH**
  Q8R
  Collaboration with Q10 Group

- **Regional** - Step by step approach
  1st : To facilitate the understanding of Q8 concepts
  Previous knowledge + QbD and Quality Risk Management
  Advanced? Prospective validation

  2nd : Implementation of design space
  Discussion with MHLW

Challenges and opportunities for ICH Q8: An industry perspective

Kimiya Okazaki, Ph.D.

Pfizer Japan Inc.

June 9th, 2006

Today's Presentation

- Quality by Design considerations in Q8
- A possible process for Design Space approach
- A case study
- Application of Design Space into Application Form

Quality by Design Considerations in Q8

- Guideline for Pharmaceutical Development
  - Reached Step 4 in Nov. 2005
  - Suggested contents for the 3.2.P.2 (Pharmaceutical Development) section of a regulatory submission in CTD format
- Quality by Design
  - Quality cannot be tested into products; i.e., quality should be built in by design.
  - Quality by Test → Quality by Design (QbD)

Adoption of Q8 delivers a new state

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- An ability to effect Continuous Improvement and Continuous "real time" assurance of quality

New Paradigms

- **Design Space**
  - Multidimensional combination and interaction of input variables (e.g., 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
- **Science-base / Risk-base**
  - Decision making based on science and;
  - Probability of occurrence of harm and the severity of that harm
- **Regulatory Flexibility**
  - Areas where the demonstration of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches
- **Continuous Improvement**
  - Quality of product should be improved thorough product-life-cycle

A possible process steps in Design Space

Step 1: List factors (i.e., quality attributes, process parameters, etc.) to be considered

↓

Step 2: Identify important factors; and
Study relationship and/or influence among the factors

↓

Step 3: Establish Design Space

↓

Step 4: Translate Design Space into manufacturing process of AF (Application Form)

Step 1: List factors to be considered

- List factors relevant to the quality and manufacture of product
  - Quality attributes
    - Drug product, drug substance, excipients, intermediates
      - e.g., potency, content uniformity, particle size, etc.
      - Where analytical method is available
  - Process parameters
    - Parameters relevant to manufacturing process
      - e.g., drying temperature, mixing time, etc.
  - Environmental factors
    - Circumstance of manufacture
      - e.g., temperature, humidity in the manufacturing room
- Like a brainstorming work

Step 2: Identify important factors; and Study relationship and/or influence among the factors

- Identify important factors
  - Quality attributes
  - Process parameters
- Relationship and/or influence among the identified factors
- Methodology
  - Experiences
  - Risk management/analysis
  - Statistics analysis
    - Experimental design, multivariate analysis, principal component analysis, Taguchi quality engineering, etc.

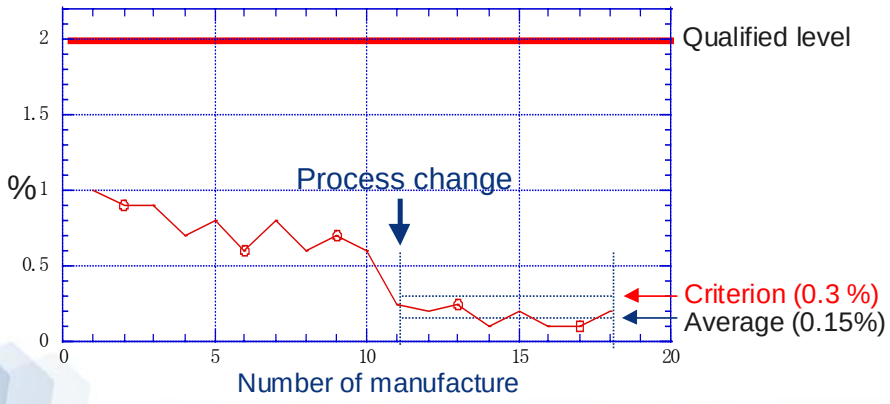
Step 3: Establish Design Space

- **Relationship and allowance of relevant factors**
  - **Relationship among factors**
    - e.g., Identified important quality attributes and process parameters
    - Some factors may come from different unit operations
  - **Allowance that can assure the quality of the product**
    - What's that mean?
    - Traditional paradigm based on Actually Measured Values → New paradigm based on safety and efficacy: Design Space approach

Traditional paradigm

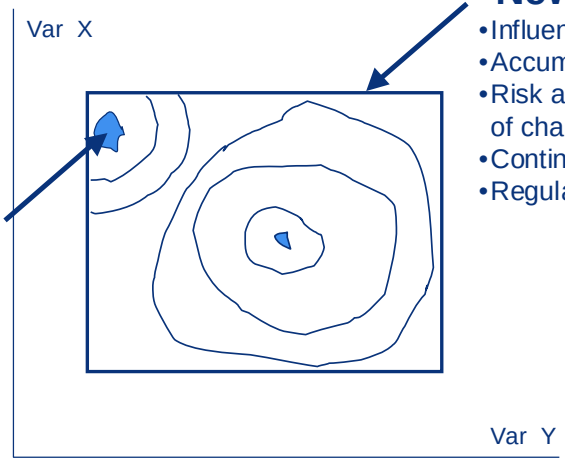
Concept of quality assurance in Japan

- **Quality assurance based on Actual Measured Values (AMV) of recent batches manufactured at/over pilot-plant scale**
  - Based on manufacturing process, facility and capability at J-NDA filing
    - AMV could be inherent values from the manufacturing method at the filing



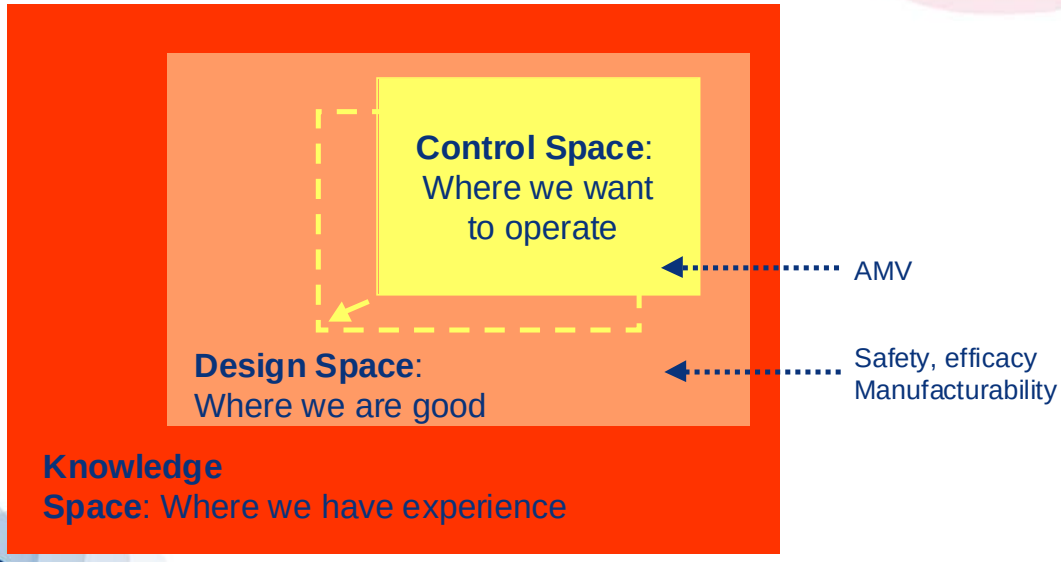
Design Space
Traditional vs. New Paradigm

New Paradigm
- Influence of factors
- Accumulate knowledge
- Risk analysis of impact of change possible
- Continuous improvement
- Regulatory Flexibility

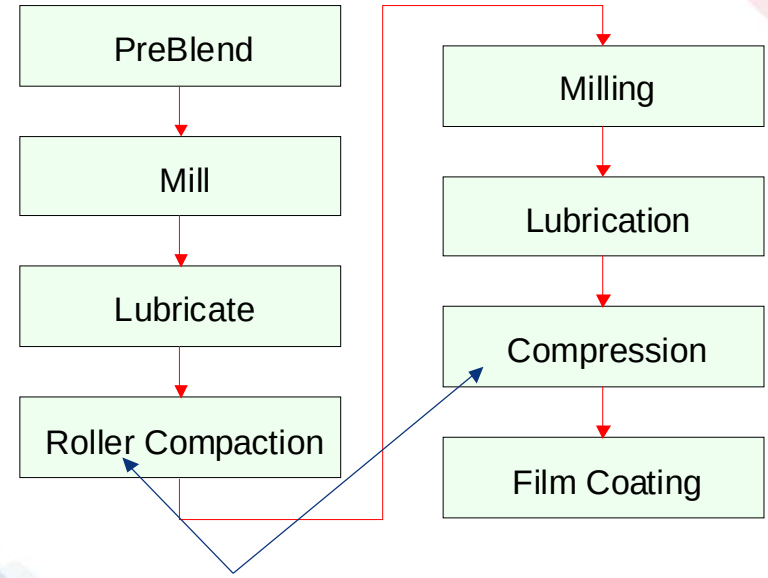


Traditional
- Limited knowledge
- 3 batches data
- Any change needs new data and new approval

New Paradigm
for establishing proposed specifications

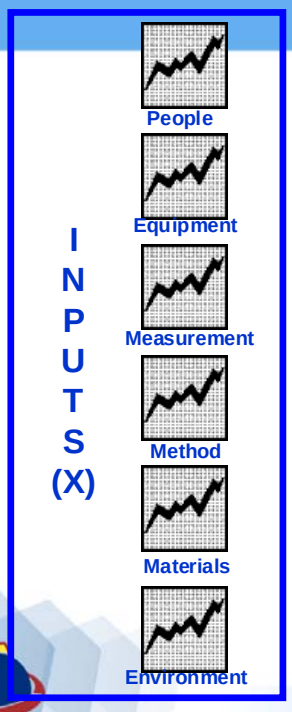


A Case Study:
Dry Granulation Manufacturing Process



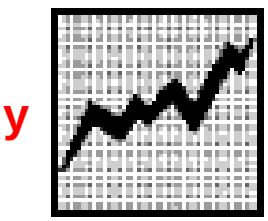
as examples

Process Understanding



$y = f(x)$

Inputs to the process control variability of the **Output**



OUTPUT

$CQA = f(KPP_1, CPP_2, \ldots KPP_i)$

Quality Attributes - 'Critical' & 'Key' (Pfizer Definitions)

- **Quality Attribute (QA)** – A physical, chemical, or microbiological property or characteristic of a material that may directly or indirectly impact product quality or the effectiveness of a process
  - Each Quality Attribute has an associated analytical method.
- **Critical Quality Attribute (CQA)** – A physical, chemical, or microbiological property or characteristic of a material, associated with an analytical method, that ***directly or indirectly impacts*** pre-defined product criteria (safety, product performance, quality & marketability)
- **Key Quality Attribute (KQA)** – A property or characteristic that ***has the potential to impact*** pre-defined product criteria (safety, product performance, quality & marketability)

Process Parameters - 'Critical' & 'Key' (Pfizer Definitions)

- **Process Parameter** – an all-inclusive term used to describe a parameter used during production to adjust or monitor the process
  - Design Space defines boundaries for each process parameter
- **Critical Process Parameter (CPP)** – A process parameter that *influences critical quality attributes* (CQA)
- **Key Process Parameter (KPP)** – A process parameter that is assessed as *having the potential to impact* product quality or process effectiveness

Roller Compaction: Impact of Roll Design Study

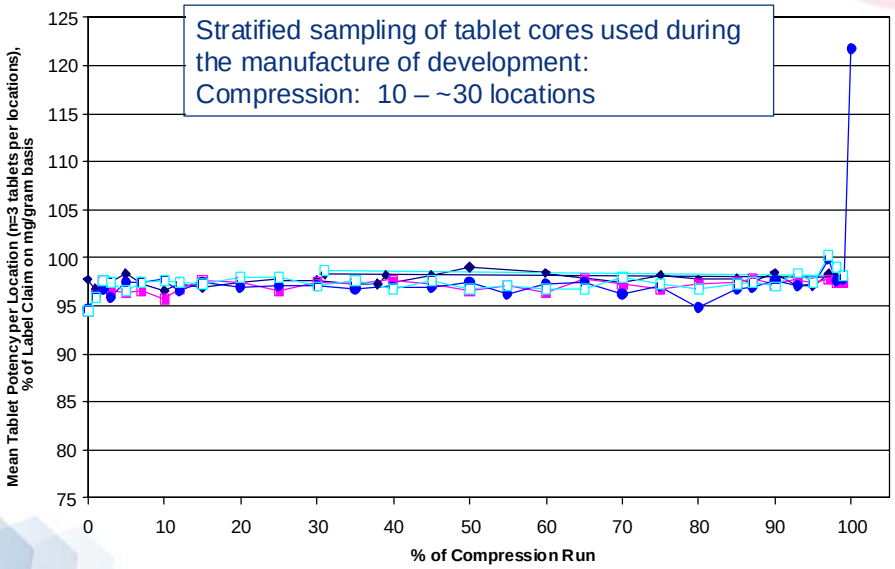
- **Studies Performed:**
  - Independent Study to Determine Impact of Roll Design
    - Purpose: Determine the impact of roll design on the characteristics of the resulting granulation
    - Variables:
      - Deep Pocketed vs. Knurled
      - Roll Force
    - Responses:
      - Particle size distribution
      - Density
      - % Bypass

Results: No impact on % bypass, granulation particle size, or density.

Summary of Roller Compaction Studies

Parameter	Boundary Results	Control	CPP / KPP
Roll Force	Target and operating range identified	Batch Record	KPP
Roll Speed	Target and operating range identified	Batch Record	No
Gap Width	Target and operating range identified	Batch Record	KPP
Granulator Screen Size	Target and operating range identified	Batch Record	KPP
Granulator Speed	Target and operating range identified	Batch Record	No
Roll Type	Deep pocket, knurled, and serrated are demonstrated	Batch Record	No

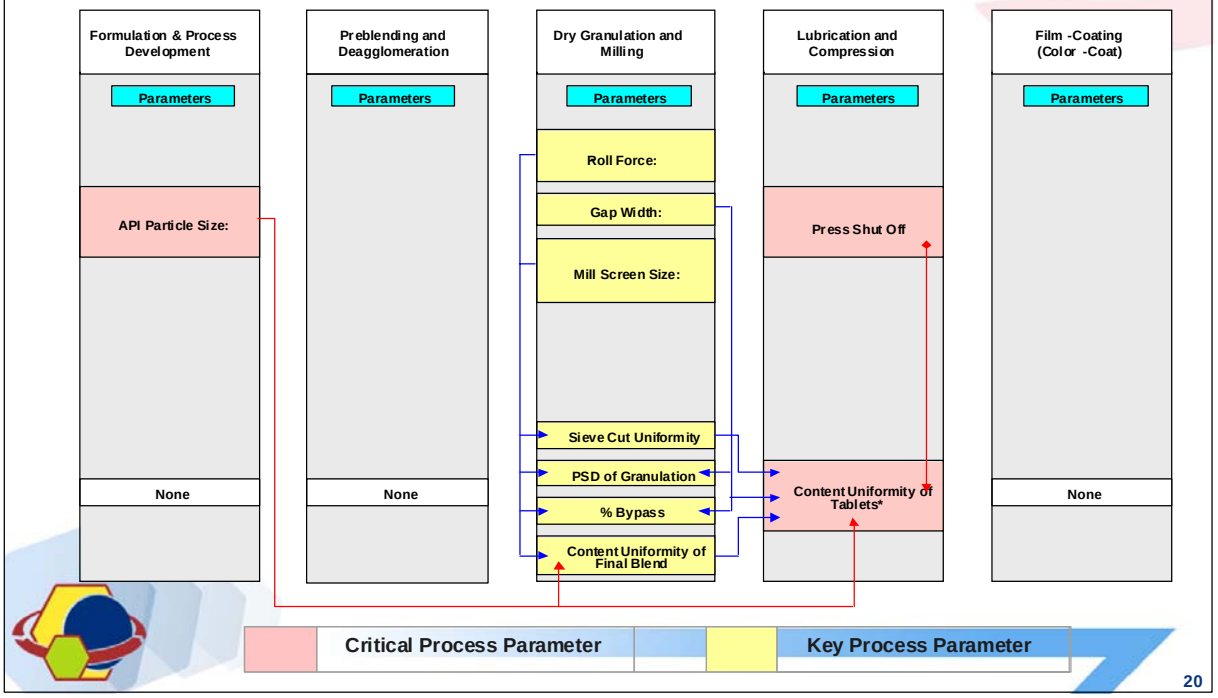
Compression: Identifying "Edge of Failure" for Content Uniformity



Summary of Compression/Content Uniformity Study

Parameter	Boundary Results	Control	CPP / KPP
Main Compression Force	Operating target and range identified	Batch Record	No
Tablet Press Speed	Operating range identified	Batch Record	No
Press Shut-Off	~ 1.8 kg blend remaining	Automatic press shut-off due to upper punch compression force variability exceeding set point, and hopper sensor	CPP
Tablet Content Uniformity	Unknown	Testing of in-process tablet cores in accordance with stratified sampling draft guidance document	CQA

A Drug Product Design Space



A possible process steps in Design Space

Step 1: List factors (i.e., quality attributes, process parameters, etc.) to be considered

Step 2: Identify important factors; and
Study relationship and/or influence among the factors

Step 3: Establish Design Space

Step 4: Translate Design Space into manufacturing process of AF (Application Form)

Step 4: Translate Design Space into manufacturing process of AF: Background

- **Manufacturing process description became regulatory agreements after implementation of revised PAL**
  - PFSB 0210001, Feb. 2005
- **Minor change is allowed under Japanese GMP**
  - Concepts of continuous improvement and regulatory flexibility have been incorporated into Japanese regulation
  - No issue may occur if manufacturing section of AF can be prepared, taking into considerations future process changes, by using Target/Set values, etc., for the process parameters relevant to Design Space
    - Although Minor change notification may be necessary

Step 4: Translate Design Space into manufacturing process of AF: Considerations

- **Significant interactions among factors**
  - In the case where there is significant interactions among more than two factors (e.g., quality attributes and process parameters) from the same or different unit operations
    - There is a condition for manufacturing process descriptions of AF where effect of each factor has to be independent
- **Design space for quality attributes and formulation**
  - In the case where design space is established for formulation and/or quality attributes directly or indirectly reflected as specification of drug product, drug substance, excipients and intermediate, etc.
    - Changes of formulation and specification are usually considered as a post-approval-change application matter

Current Pfizer Approach for Linking Design Space and J-PAL AF Concepts

Classification in Design Space	Proposed Change Control System	Description in AF
CQA and CPP	"Post-approval change (major change) application" matter	Description with 《 》 or without any brackets
KQA and KPP	"Minor change notification" matter	Description with 『 』 or " "
Non-CQA and CPP/non-KQA and KPP	Internal change control	Not describe in AF at all

Challenges for ICH Q8

- **Edge of failure**
- **Manufacturing description for AF**
  - Connection between established Design Space and manufacturing description for AF
  - Design Space of quality attributes
- **Update of Design Space**
  - Much more knowledge after launch
- **Methodologies or procedures for establishing ICH Q8 may already be available**
  - Many methodologies to efficiently and securely evaluate many factors relevant to formulation development have been proposed

Opportunities

- Necessity of more extensive data in development phase
  - More resources in development phase
- However, it may be an opportunity…
  - Regulatory Flexibility
    - Investment to future businesses to improve quality and efficient change control
- Universal Quality System: Quality by Design
  - Cooperation of regulatory agencies and industry
  - Cooperation in ICH regions

Acknowledgments

- Roger Nosal
- Kieran Dignam
- Shigeru Hayashi
- John Berridge
- Robert Baum
- Charles Hoiberg
- Jim Spavins
- Jeff Blumenstein
- Hatsuki Asahara
- Toshiyasu Yamada