

ENGINEERING PHARMACEUTICAL INNOVATION



**Welcome to
The Fifth Pharmaceutical Quality Forum
Symposium**

第5回医薬品品質フォーラムシンポジウムへようこそ

Co-sponsored by ISPE

ISPE国際本部共催

Charles P. Hoiberg, Ph.D. (チャールズ P.ホイバーグ Ph.D.)

Secretary, ISPE International Board of Directors

(ISPE国際理事、書記局長)



Core Purpose

Developing innovative professionals globally to achieve technical and operational excellence in the Pharmaceutical Industry.

Vision Statement

The Society will lead the integration of Industry Professionals, Academia, and Regulatory Agencies worldwide to achieve real innovation and understanding in the pharmaceutical industry.

ISPE Facts (ISPEとは)

- Founded in 1980 (1980年に創立)
- Not-for-profit (非営利団体)
- More than 23,000 Members in 81 countries (81カ国2万3千人以上の会員から成り立っている)
- Focused on education, information exchange, and technical documents for Industry (製薬産業向けの専門技術教育、情報交換ならびに関連技術書の作成を活動の基幹にしている)
- Excellent relationship with regulators globally (世界中の規制当局と極めて良好な関係を構築している)

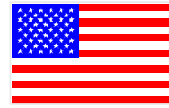
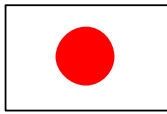
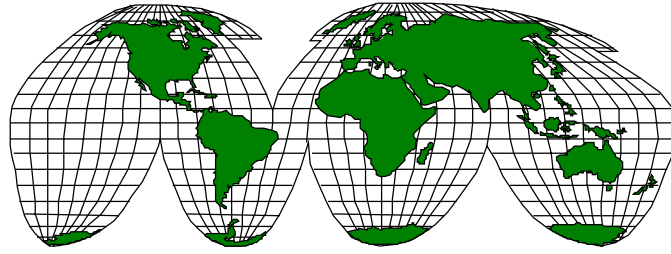


ISPE Affiliates Worldwide (ISPEは世界中に活動を拡大しております)

- Asia Pacific Affiliates (アジア太平洋地域の各国本部)
 - **Japan (日本本部)**
 - Australasia (オーストラリア):
 - Brisbane Chapter (ブリスバーン支部)
 - Melbourne Chapter (メルボルン支部)
 - New Zealand Chapter (ニュージーランド支部)
 - Sydney Chapter (シドニー支部)
 - India (インド)
 - Singapore (シンガポール)
 - Thailand (タイ国)



ICH QUALITY GUIDELINES



ICH Q8 Update

Fritz Erni
EFPIA

9.6.2006
PQF/ISPE

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Outline

- What is Q8
- Q8 as a Door Opener for
 - Describing Quality by Design
 - Including more Science and Risk Management
 - Including PAT
 - Include Design Space
- Introduces the concept of Design Space
- Describes how to define what is critical
- Redefines what is a Change
- Quality Risk Management supports the Control Strategy
- Summary

Fritz Erni

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What is ICH Q8!

- Guideline for the description what is in P2
- Describes the minimal Standard for P2
- Opens door to get closer to the
‘Desired State’
 - Science based
 - Includes Risk Management
 - Continuous improvement
 - Real Time Release
- Is Part of the New ICH Q's (Q8,Q9,Q10)

ICH Q8

Door opener for
Quality by Design



Desired 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 Continual Improvement and continuous "real time" assurance of quality

P2 Content per CTD-Q

1. Drug substance
 - Key physicochemical characteristics
 - Compatibility
2. Excipients
3. Drug product
 - Rationale for type of product
 - Formulation development
 - Overages
 - Physicochemical and biological properties
 - Performance testing
4. Manufacturing Development
5. Container closure system (and delivery devices)
6. Microbiological attributes
7. Compatibility

Where to put information in on :

- Quality by design
- Science
- Process and Formulation Understanding
- Risk Management
- Continuous improvement
- Real Time Release

When to update the documents

Fritz Erni

Where do we stand?



- Q8 Step 4 signed by 6 ICH partners and observers



- Clarifying 'baseline' and 'optional' expectations



- Enables Quality by Design and enhanced process understanding



- Outlined areas of potential regulatory flexibility that could be expected when presenting 'optional' information

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Q8 General Concepts

QbD and Risk Management

- The Pharmaceutical Development section provides an opportunity to present the **knowledge gained through the application of scientific approaches and quality risk management** to the development of a product and its manufacturing process.

Q8 General Concepts

What is minimal requirement

At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are **critical to product quality** should be determined and **control strategies justified**.

Q8 General Concepts

What is critical?

Critical formulation attributes and **process parameters** are generally identified through an assessment of the **extent to which their variation** can have **impact on the quality of the drug product**.

Q8 General Concepts

Optional Understanding

In addition, the applicant can choose to conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters.

Q8 General Concepts

What we get in return

This scientific understanding facilitates establishment of an **expanded design space**. In these situations, opportunities exist to develop more flexible regulatory approaches, for example, 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.

Possible Regulatory Flexibility

Continuous Improvement

Real time release

Reduced or elimination of routine **end product testing**

Expanded design space

Independence on **scale**
Independent of **equipment**
Independent of **site**
Independent from **drug substance** manufacturing if within spec

Process Validation

Process validation replaced by **Concurrent Process Verification** using validated methods (qualified controls)

Stability Testing

Reduced **confirmation stability** studies for any changes within the design space
Reduced **annual stability** batches

Q8 General Concepts

Review - Inspection

The Pharmaceutical Development section is intended to provide a comprehensive understanding of the product and manufacturing process **for reviewers and inspectors.**

Q8 Strategic Questions :

Submissions and Post Approvals

It is first produced for the original marketing application and **can be updated** to support new knowledge gained over the **lifecycle** of a product

Process and Formulation Understanding

Key for making a good P2 story!



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Q8 Strategic Questions :

What is the **Design Space?**

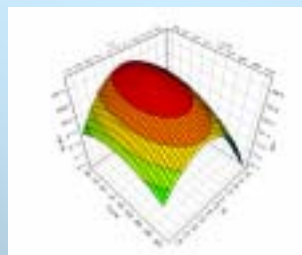
**Will be the Base for Continuous
Improvement!**

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

- Is Key for claiming **Process Understanding**
- Process understanding is Key for **Quality Risk Management**
- QRM is the base for any **Control Strategy**



Q8 Design Space :

Redefines what is a **Change?**

Base for all Post Approval Changes

Control Strategy

- **Justification of necessary controls**
 - In-Process Controls
 - End Product Controls (if necessary)
- **Based on Process and Formulation Understanding**
- **Drives the Process in the Design Space**
- **Based on Quality Risk Management**
- **To ensure conforming Quality according Specifications**

ICH Q8 : Important Points

- No escalation of requirement
 - Defines **Baseline**
 - Defines **optional** opportunities
- Open the door for submitting **Quality by Design** data
- **Optional Update** of P2 for adding knowledge for PAC
- Defines : What is a **critical parameter**
- **Design Space**: What is/is not a change
- **Regulatory Flexibility** leading to
 - Continuous improvement
 - Real time release

Q8 Next steps

As agreed in Concept Paper, Q8 is a 2 part guideline

Part 1

- Core document
- Baseline expectations
- Optional information
- Regulatory Flexibility

Step 4: Chicago
November 2005

Part 2

- Annexes relating to specific dosage forms
- Appropriate examples of risk management

First Drafting: Brussels 2005

Q8(R): Our vision

Prepare an addendum to Q8 on specific dosage forms

- Forms as Q6a (solid oral, liquid oral, parenterals)
- Format as Q8 incorporating points to consider pertinent to specific dosage form types
- Focus on exemplifying Quality by Design concepts to enhance product and process understanding and encourage Industry's sharing with Regulators.
- If possible, references to the opportunities to use relevant tools from Q9 in the appropriate sections of Q8 but not to give specific case-study examples

How Q8(R) we will proceed

- **Change our focus to solid oral dosage forms ONLY for the present**

Because it provides the greatest opportunity (lots of background and expertise) and is most common dosage form

- **Articulate the baseline (perhaps by use of case study)**
- **Illustrate QbD principles by use of examples, ensuring that we are clear on Design Space (e.g. drawn from EFPIA mock P2 document)**
- **When oral solids agreed, we will address the other types of dosage form**

Because we ought to consider the risk - benefit

Summary

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- Introduces the concept of Design Space
- Describes how to define what is critical
- Redefines what is a Change
- Quality Risk Management supports the Control Strategy

MHLW Reviewer's view

- Incorporating Design Space thinking
into a submission -



Tamiji Nakanishi
Pharmaceuticals and Medical Devices Agency
Tokyo, JAPAN

Outline

- ❑ Japanese CMC Review and Approval system
 - ❑ Reviewer's views for Design Space
 - ❑ Future perspective
-



Japanese CMC Review system

- J-NDA application Form
 - Approval Matters

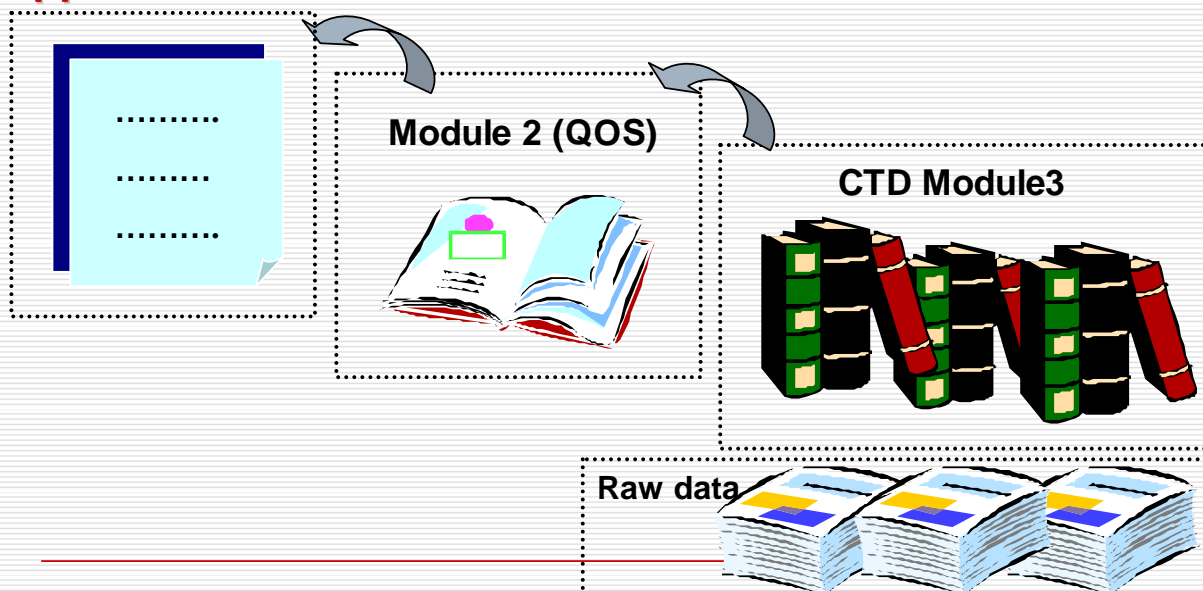
 - Post Approval Changes
 - Partial Changes
 - Minor Changes
-



Japanese CMC Review system

- J-NDA Application Form and CTD -

Application Form



J-NDA Application Form

- Under Pharmaceutical Affairs Law
 - Contents provided in J-NDA **Application Form**
 - are dealt with as “matters subject to approval”
 - Contents described in **Approved Application Form**
 - are “legal binding” approval matters
 - Used for pass-fail decision



J-NDA Application Form

-Approval Matters-

- General Name
- Brand Name
- Composition
- Dosage and Administration
- Indications
- Manufacturing Process including control of materials**
- Specifications and analytical procedures**
- Storage condition and shelf-life



J-NDA Application Form

- Drug Product -

- All process from the raw material(s) to the primary packaging process
 - A flow **diagram** of manufacturing process
 - Raw materials
 - Charge-in amount
 - Solvent
 - Intermediate materials
 - Yield
 - Process Parameters
 - A **Narrative description** of manufacturing process
-



J-NDA Application Form

Narrative Description of Manufacturing process

- Matters needed for assuring the product quality should be selected
 - Quantities of raw materials, equipment, processes, process parameter, process control (speed, time, temp., pressure, pH, etc)
 - Test and acceptance criteria of critical process and intermediate
 - Identity and specification of primary packaging material (or manufacturer and type number of the packaging material)
-



Post Approval Change

- "Minor Change" system -

Post-approval Change to Approval matter

- Partial Change
 - prior-approval change submission

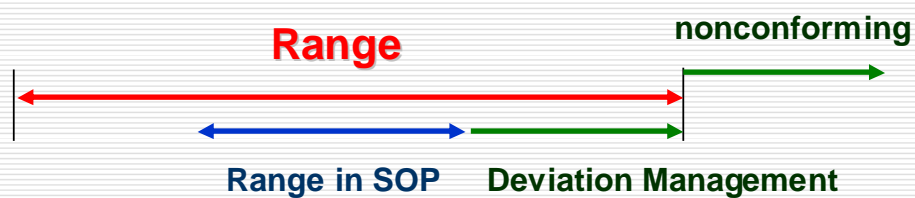
 - Minor Change
 - Notification within 30days of change
 - Data held at site
-



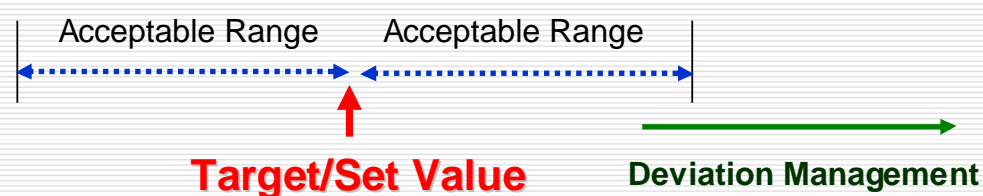
J-NDA Application Form

- Process parameters -

Range



Target/Set Value



Reviewer's view for Design Space

- Design Space
- Design Space and “Minor Change” System



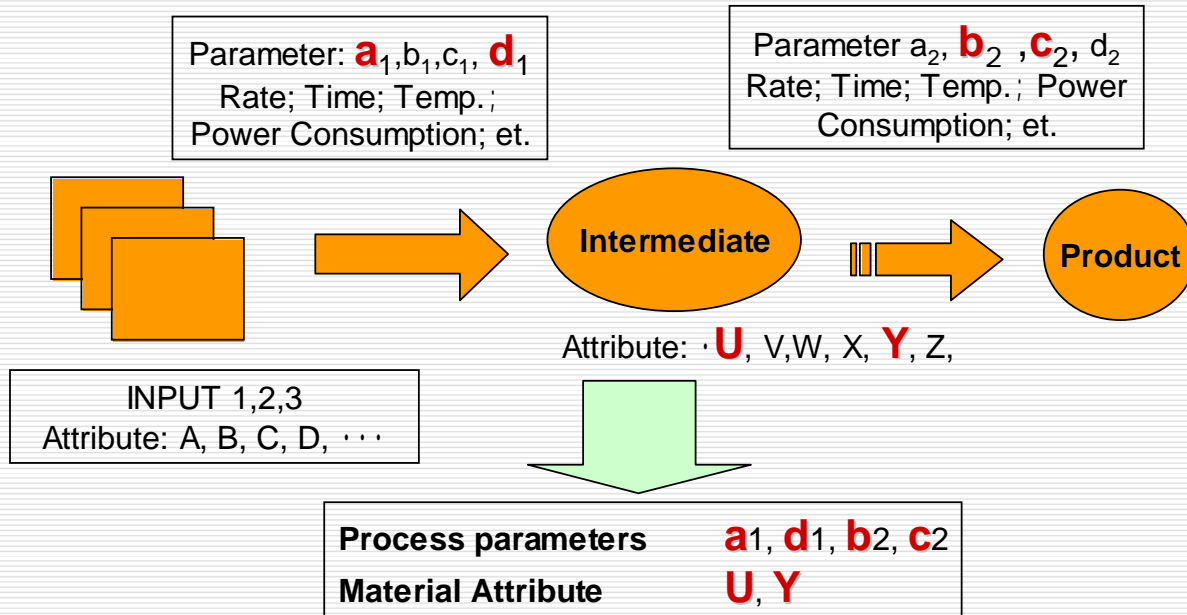
Design Space

- The **multidimensional combination and interaction** of 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 subjected to regulatory assessment and approval.



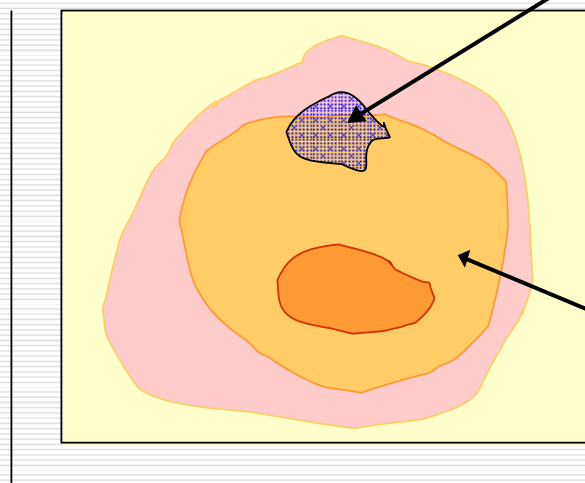
Design Space

- Scientific Understanding of critical process parameters and product attributes -



Design Space

Y



Traditional Process

- limited knowledge (3 batches)
- Any changes need prior-approval change submission

Design Space

- Movement in the design space is not a change

X



Design Space and Minor Change system

	"Minor Change" system	Design Space
	Target/Set value Range	Multidimensional combination and interaction
Variables	Process Parameters, Material Attributes	
Variables - Exception-	<input type="checkbox"/> Formulation composition <input type="checkbox"/> etc...	<input type="checkbox"/> Nothing?
Post Approval Change	Movement <input type="checkbox"/> Within not a change? <input type="checkbox"/> Outside Minor/Partial Change	Movement <input type="checkbox"/> Within not a change <input type="checkbox"/> Outside a change
Deviation	<input type="checkbox"/> Deviation management in GMP	<input type="checkbox"/> Failure (?)



Design Space and Minor Change system - Status quo -

- "Minor Change" system facilitate Design Space paradigm

	Range	Target/Set Value
Partial Change		
Minor Change		

- However,
 - Ranges to be approved is limited
 - Except for
 - interacting parameters
 - Formulation composition



Design Space and Minor Change System

- What needs to be changed -

Consistency with Minor Change System

	Range	Target/Set Value
Partial Change		
Minor Change		

- Post-Approval Change Process for Design Space
 - Movement out of Design Space
-



Movement out of Design Space

- How should it be addressed? -

Is Risk-based approach applicable to post-approval change process for Design Space?

If possible:

- **Low-risk:** Minor Change
Notification within 30days of change
 - **High-risk:** Partial Change
Prior-Approval change submission
-



Future perspective

- Issues to be solved -

- QOS and J-NDA Application Form
 - Review and Inspection
 - Regulatory flexibility
-



QOS and Application Form

- Primary Review Document and Approval Matters -

- What kind of information can lead to establishment and justification of the Design Space
 - Refer to Q8(R) guideline
 - How to describe in Application Form
 - Approval Matters in J-NDA Application Form
 - Life cycle management of P2
-



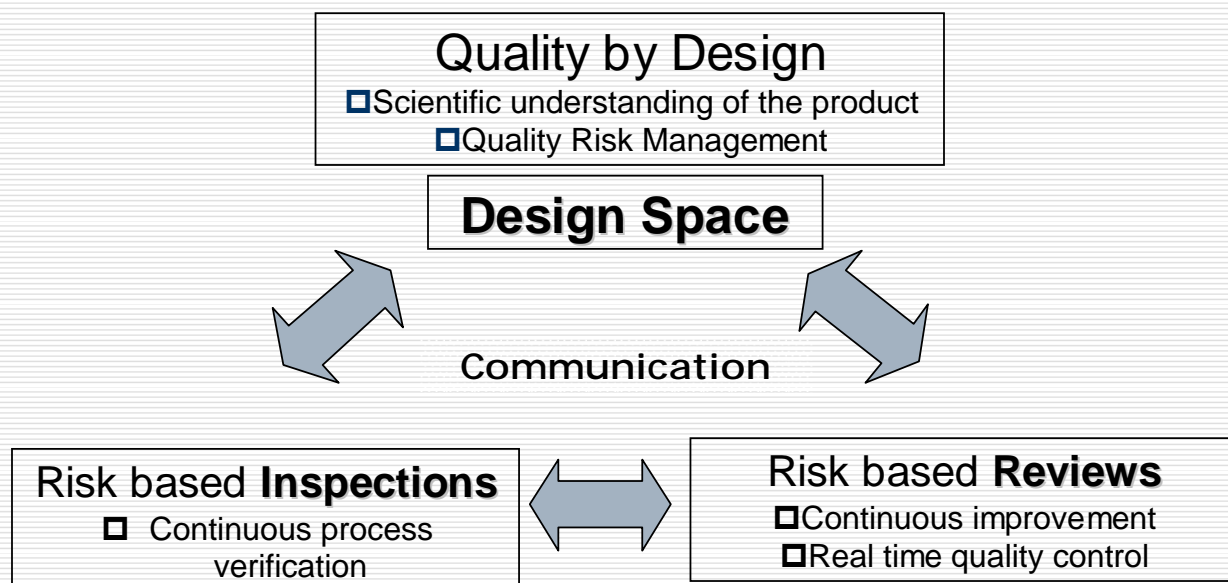
Review and Inspection

□ Movement in the agreed design space is not a change

■ Review & Inspection Process



Review and Inspection communication



Regulatory flexibility

- ❑ Reduction of post-approval submission
- ❑ Real-time quality control, leading to a reduction of end-product release testing



Thank you for your attention



Incorporating Design Space (DS) Thinking into a Submission EU's view

Susanne KEITEL, Ph.D.
Jean-Louis ROBERT, Ph.D.



Yokohama, 10 June 2006

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Overview of the Presentation

- ICH Q 8: background; EU experience
- Design Space
- Associated guidelines
- Submission in applications
- Some examples
- Conclusion

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Structure of ICH Q 8

"Part 1"	"Part 2"
Core document	"Annex" relating to specific dosage form
Baseline expectations	Examples of "baseline expectations" vs. "optional information"
Optional information	Reference to the use of Q 9
Definition of Design Space	
Regulatory flexibility	

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Pharm. Dev. – EU Point of View

Pharmaceutical development studies...

- are the basis for any sound development activities for a drug product
- should form the risk analysis of the suitability of a formulation and its manufacturing process
- should identify any weak points in the formulation or its manufacturing process
- should provide sufficient assurance that the product can be reproducibly manufactured in the specified quality
- ...

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The Concept

ICH Q 8- Pharmaceutical Development

- aim: to design a quality product and manufacturing process to consistently deliver intended performance of the product.
- comprehensive understanding of product and manufacturing process for reviewers and inspectors
- first produced for original marketing application, may be updated to support new knowledge gained over the lifecycle of a product
- can be a basis for quality risk management

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The “Two Tiered System”

Clear distinction between “baseline expectations” and “opportunities”



It is entirely the applicant’s decision how much resources to invest and at which time in a product’s life-cycle!

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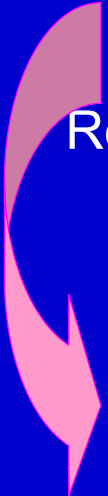
Baseline Expectations

At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified....

....Critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can have impact on the quality of the drug product.

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EU: Baseline Expectations




Requirements as outlined in the present
CPMP/QWP Note for Guidance on
Development Pharmaceuticals
to be met in general

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Enhanced Understanding

Applicant can **choose** to conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters

 **opportunity** to demonstrate higher degree of understanding of material attributes, manufacturing processes and their controls

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Enhanced Understanding

Applicant should demonstrate enhanced knowledge of product performance

Understanding can be gained by application of, e.g., formal experimental designs, process analytical technology, and/or prior knowledge

Scientific understanding facilitates establishment of expanded design space, potentially leading to opportunities to develop more flexible regulatory approaches

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Enhanced Understanding

- ☺ Risk-based regulatory decisions
- ☺ Manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review
- ☺ Reduction of post-approval submission
- ☺ Real-time quality control, leading to a reduction of end- product release testing

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Design Space as defined in Q8

“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 generally considered as a change....

12

Design Space as defined in Q8

... 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.”

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What can Design Space be?

- “one dimensional”: no investigation on impact of varying process parameters, material from one source only

=> very baseline approach,
no change without variation

Would this approach be acceptable at all??

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What can Design Space be?

- “multi dimensional”: covering all aspects of formulation and/or process development
- => enhanced understanding,
regulatory flexibility within design space,
basis for continual improvement without
prior regulatory approval

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What can Design Space be?

- selected aspects, e.g. different sources for one excipient, robustness assessment of selected process parameters
- => baseline approach, limited flexibility

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How can Design Space be Achieved?

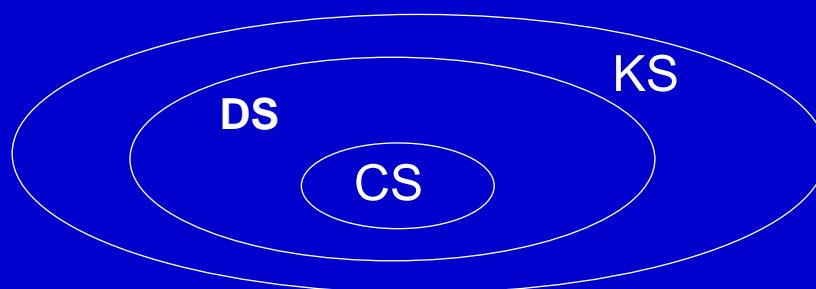
Formal pharmaceutical development studies
vs.

- prior experience/knowledge
or
- experience gained in the production phase

It is up to the applicant/MAH to decide!

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Control-, Design- and Knowledge Space



CS: Control space

DS : Design space

KS: Knowledge space

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DS : Associated guidelines

- Q9: Quality Risk Management
- Q10: Quality System

Q9: Quality Risk Management

- Two primary principles of quality risk management are:
 - The evaluation of the risk to quality should be based on scientific knowledge (Q8) and ultimately link back to the protection of the patient.
 - The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

QRM (Q9) as Part of Development

- To design a quality product and its manufacturing process to deliver the intended performance of the product (Q8)
- To enhance knowledge of product performance over a wide range of material attributes, processing options and processing options and process parameters
 - Assessment of critical attributes of raw materials, solvents, APIs starting materials, excipients, packaging materials
 - Establishing of appropriate specification and manufacturing controls
 - Decrease of variability of quality attributes
 - Assessment of need for additional studies relating to scale up and technology transfer
 - To make use of the design space (**DS**) concept

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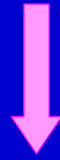
Q10: Objective/Scope

- Describe the modern quality system needed to establish and maintain a state of control that can ensure the realisation of a quality drug product and facilitate continual improvement over the life cycle of a drug product.
- It should promote a paradigm shift from discreet GMP compliance systems at each stage of the product lifecycle to a global QS approach over the entire lifecycle of the product.

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Q8, Q9, Q10: Linkage

Quality by Design + Quality Risk Management + Modern Robust Quality System



Lower Risk Operations
Innovation
Continual Improvement
Optimized Change Management Process

DS Submission (1)

- Submission of the **DS** could be divided in two parts:
 - Presentation (overview) of the concept or overall strategy (introduction);
 - Presentation of the studies and rationale supporting **DS**.

DS Submission (2)

- Issues to be considered:
 - Definition of the step where the **DS** is applicable
 - Full manufacturing process
 - Distinctive operation unit e.g. fluid drying operation
 - Indication of the parameters considered in the **DS** :
 - Identification of critical parameters or steps (quality risk management approach)
 - Input variables
 - Process parameters
 - Process controls

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DS Submission (3)

- Issues to be considered (cont'd.):
 - Evaluation
 - indication about the mathematical model used:
design of experiments, multivariate data analysis (MVDA),
factorial design;
 - Possible conclusion/outcome
 - Relation **DS** and quality attributes
 - Process scale or equipment independent ?
 - No stability commitments (?) or follow-up necessary ?
 - No release testing any more ?
 - No conventional process validation anymore ?
 -

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DS : Benefit - Opportunity

- Flexibility on
 - properties of input materials
 - the manufacturing process i.e. fewer variations
- More intensive development is needed:
 - More knowledge about the process and product
 - Robustness of the process and product
 - Enhanced process monitoring (PAT concept)
 - Improved product quality

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Examples of problems occurring when having insufficient development

- Appearance of a new polymorphic form (pm).
- Manufacturing process: scaling up
 - 2 products not marketed: manufacturer was unable to manufacture production scale batches;
 - 3 variants of a medicinal product (combination ds/dp of pilot scale and production scale) were not bioequivalent.
- Change of drug substance supplier
 - 2 batches manufactured by using different drug substance suppliers were not bioequivalent.

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Conclusion

- New concept or only formalisation of existing concepts?
- Workshop will hopefully bring some answers to the questions raised by both industry and regulators
- EU Regulators are positive about the concept of the **DS**

ISPE, Yokohama, Japan
June 9, 2006



Implementation of ICH Q8 and QbD – An FDA Perspective

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



Outline

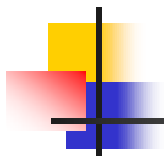
- ICH Q8
- FDA's implementation of Q8
- FDA's view on quality by design (QbD)
- QbD system for pharmaceutical development
- FDA CMC (chemistry, manufacturing, & controls) Pilot Program
- Summary



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

3



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

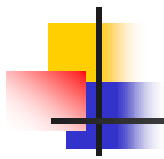
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FDA's Implementation of Q8

- 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

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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

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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

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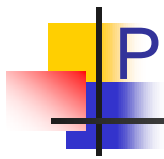




FDA's View on QbD

- 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

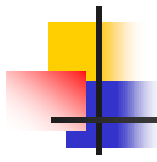
9



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

10



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

11



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

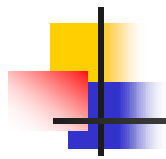
12



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

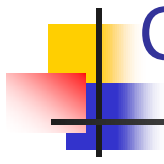
13



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)

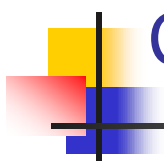
14



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

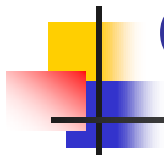
15



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

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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

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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?

18



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

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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?

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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

21



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

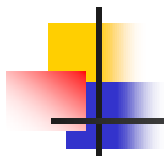
22



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

23



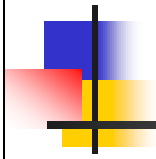
Summary

- 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

24

Pharmaceutical Quality Forum: 5th Symposium, Yokohama

June, 2006



Design Space

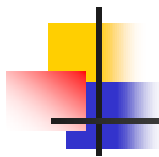
Japanese Industry's Perspective



Kazuhiro Okochi

JPMA Q8 deputy topic leader

Takeda Pharmaceutical Company Ltd.



Content of the Presentation

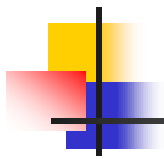
- 1 Background
- 2 Discussion on Design Space
 - Design Space for manufacturing process
 - Design Space for formulation attribute
- 3 Revised Pharmaceutical Affairs Law
- 4 Proposal from JPMA
- 5 Conclusion



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

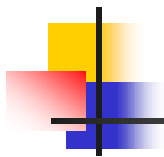


Design Space

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.

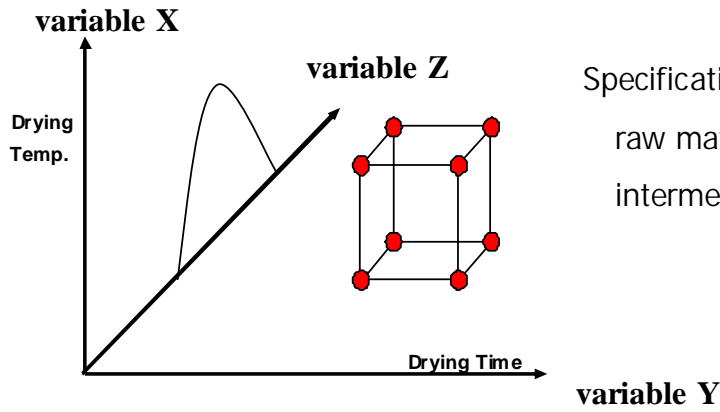
Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

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.



Toward the end of Desired State

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)

Knowledge, Process Understanding



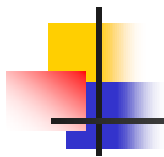
Japanese Pharmaceutical Affairs Law

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:

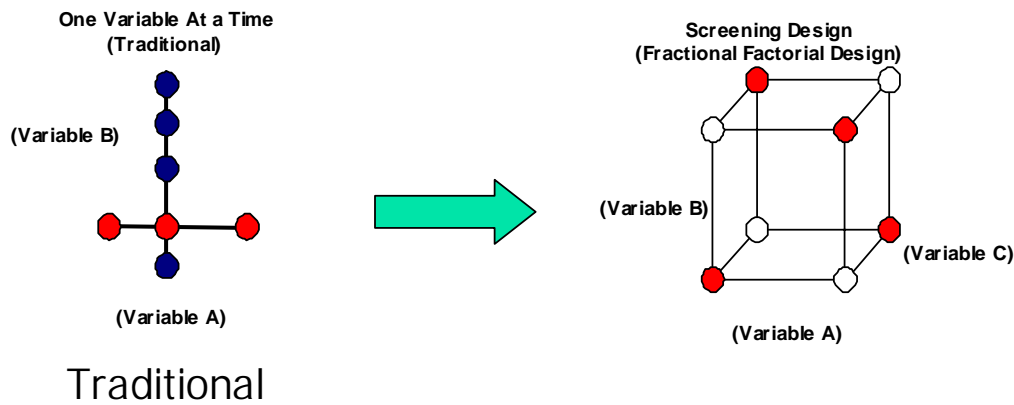
A permissible range should be specified in the format for approval.



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](#)”.



Design of Experiment

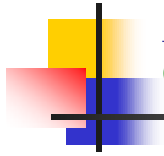
Example Manufacturing Parameters
Case Study in Takeda

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

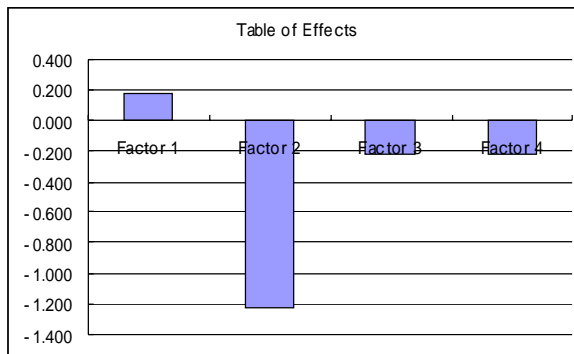


Example Manufacturing Parameters
Case Study in Takeda

Multivariate Analysis
Determining which
parameters drive effects

Met Specification

Content, Content Uniformity,
Dissolution etc



Design Space would be

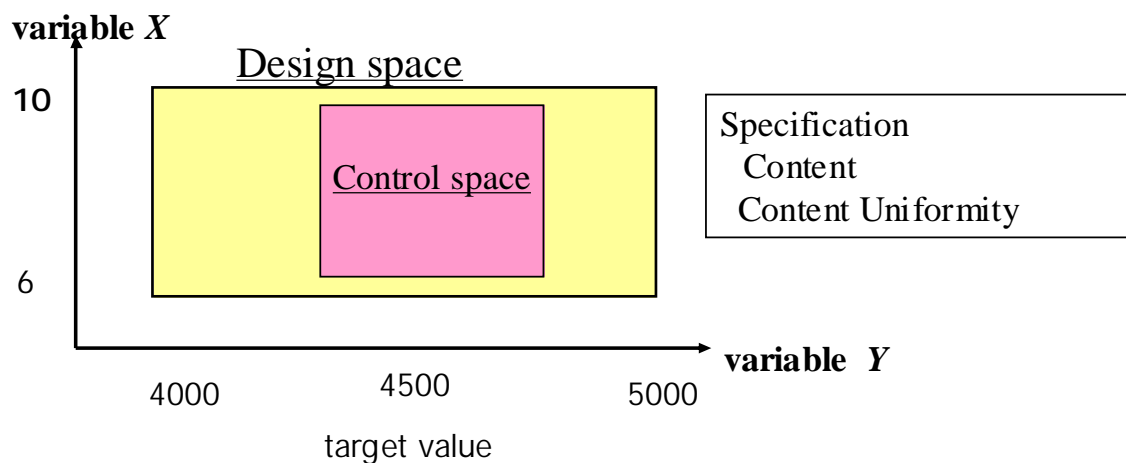
Parameter 1: 4000 - 5000

Parameter 2: 6 - 10

Parameter 3: 70 - 80

Parameter 4: 360 - 420

Design space VS Control space



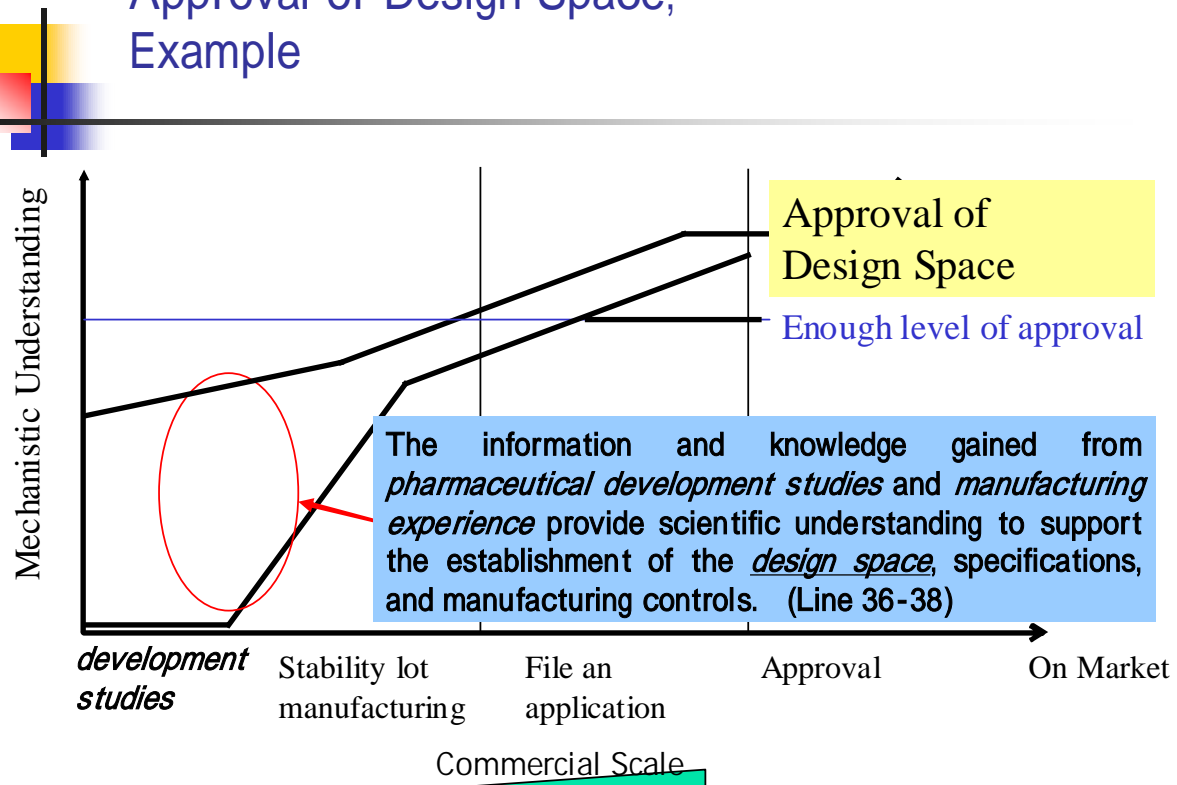
Need to make clear the relation with Design Space and

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

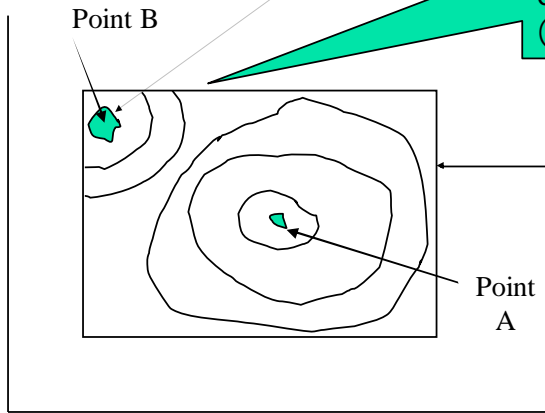
ICH Q8 London meeting (March 2004)



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)

variable X



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

variable Y

Previous Process Study

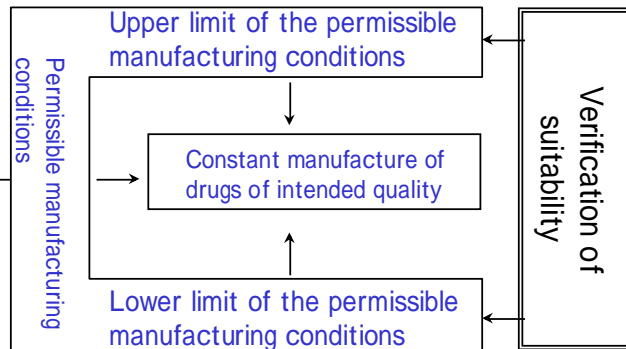
Results of study for industrialization

Past production records of similar products

Identification

Variation factors

Prospective Validation



· Physical properties of raw materials

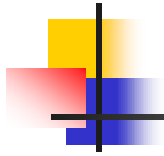
· Operating conditions etc

Quality of products

薬食監麻発0330001号
Validation Standards

Definition of Prospective Validation

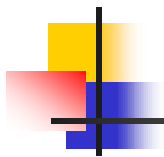
Acknowledgments: Tadatsugu Tanino, Ph. D. Shionogi & Co. Ltd.
(Slide is revised for English referred with "The Japanese GMP Regulations 1998, YAKUJI NIPPO, LTD.)



JPMA Proposal

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

- 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



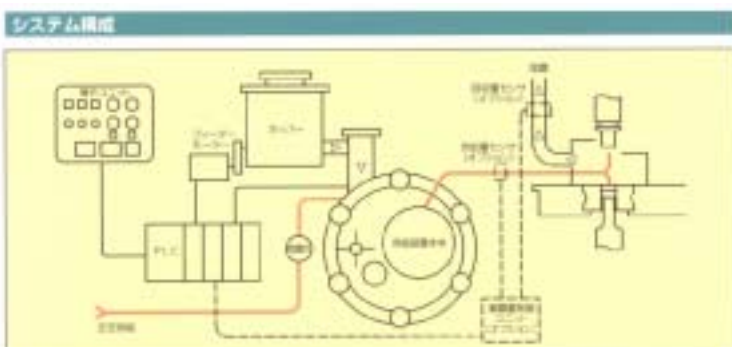
Design Space for Formulation Attributes Examples of Lubricant

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 “Biryō”

(Example 2) 0.21 ~ 1.16 %

Opportunities for More Flexible approach !

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

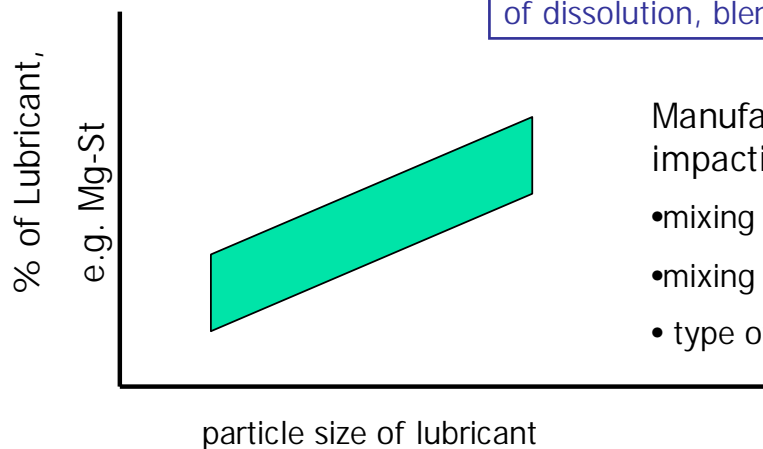
IPJ-2 (INTERPHEX JAPAN May 17 2006)

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



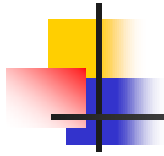
Design Space for Formulation Attributes Examples of Lubricant

Assurance of quality by in-process monitoring of dissolution, blend uniformity, ...



Manufacturing conditions impacting ‘Quality’

- mixing time
- mixing scale
- type of blender



Design Space for Formulation Attributes

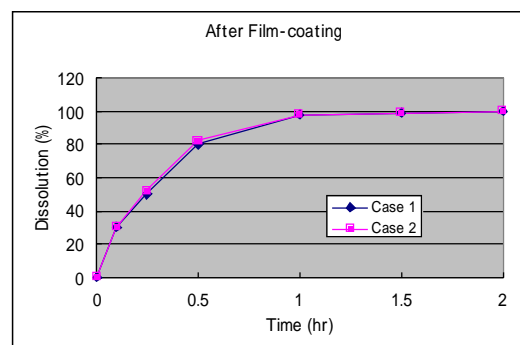
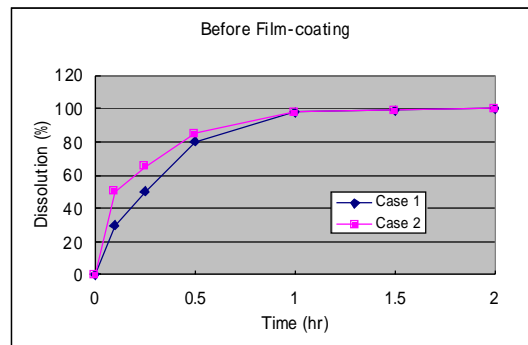
Examples of coating material

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



0

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



1

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)



2

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**



3

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 through product-life-cycle



4

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)



5

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**



6

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.



7

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

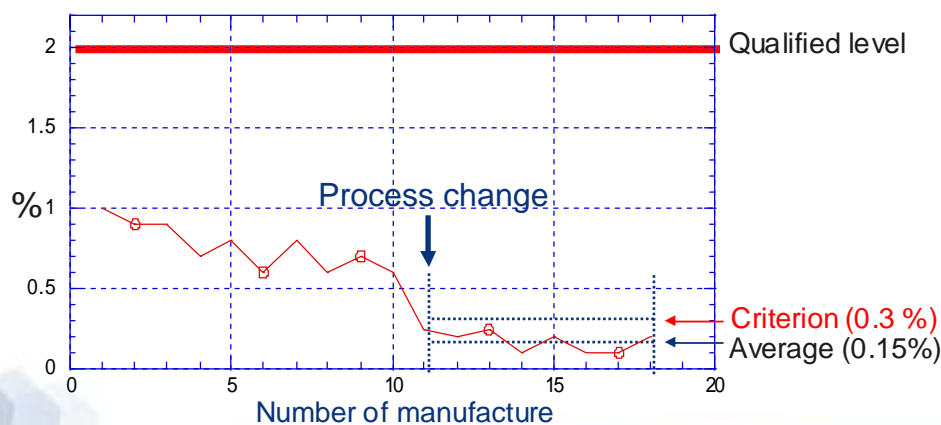


8

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



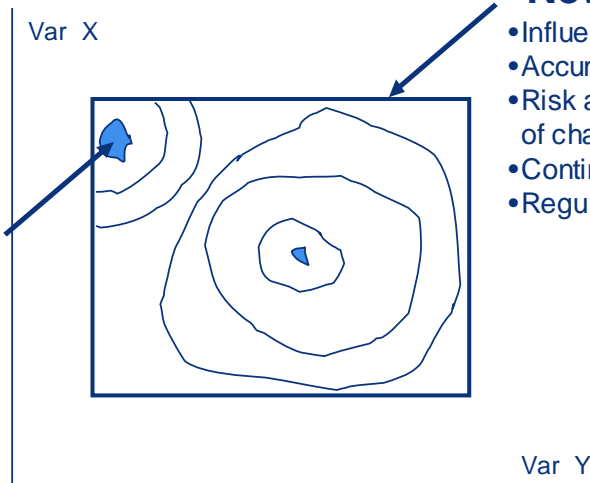
9

Design Space

Traditional vs. New Paradigm

Traditional

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



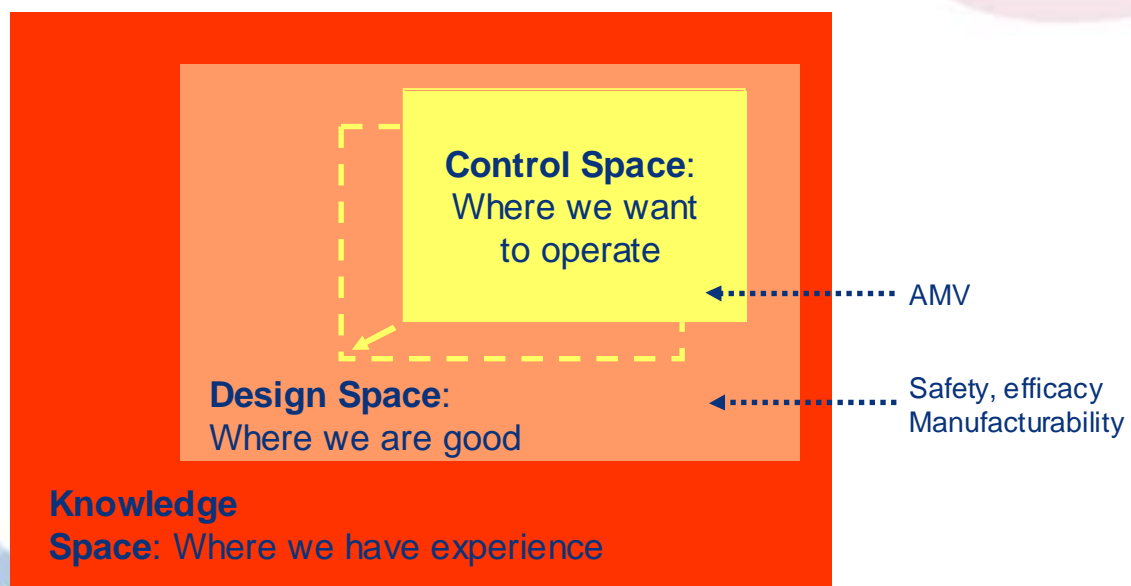
New Paradigm

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

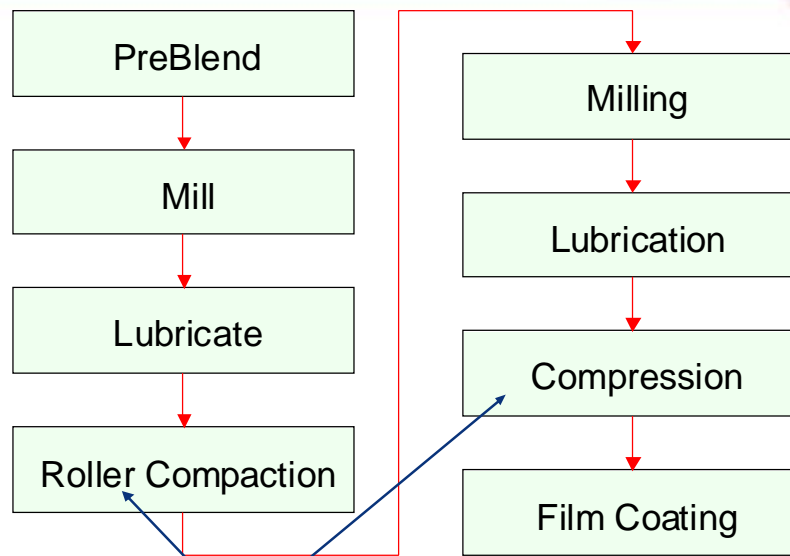


New Paradigm

for establishing proposed specifications

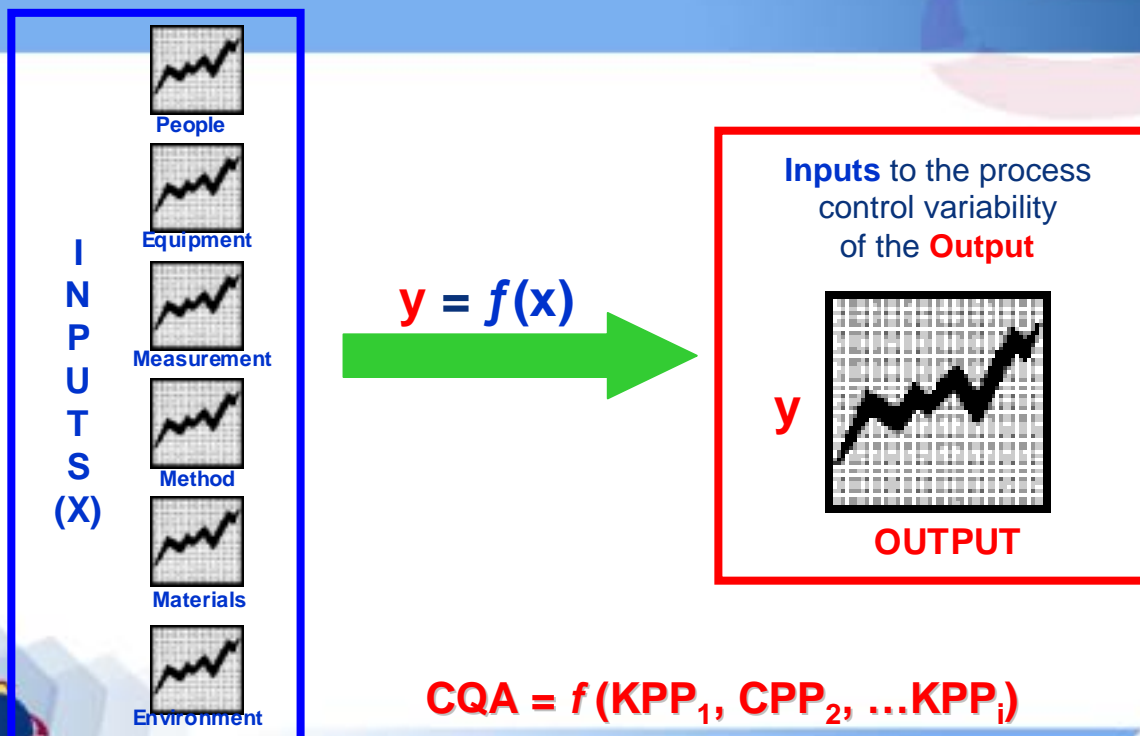


A Case Study: Dry Granulation Manufacturing Process



as examples

Process Understanding



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)



14

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



15

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.



16

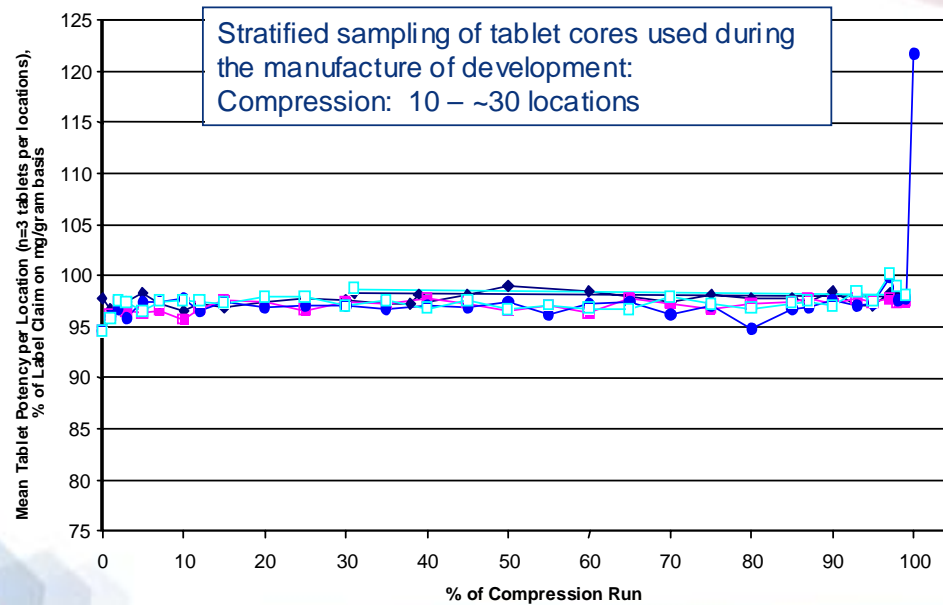
Summary of Roller Compaction Studies

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



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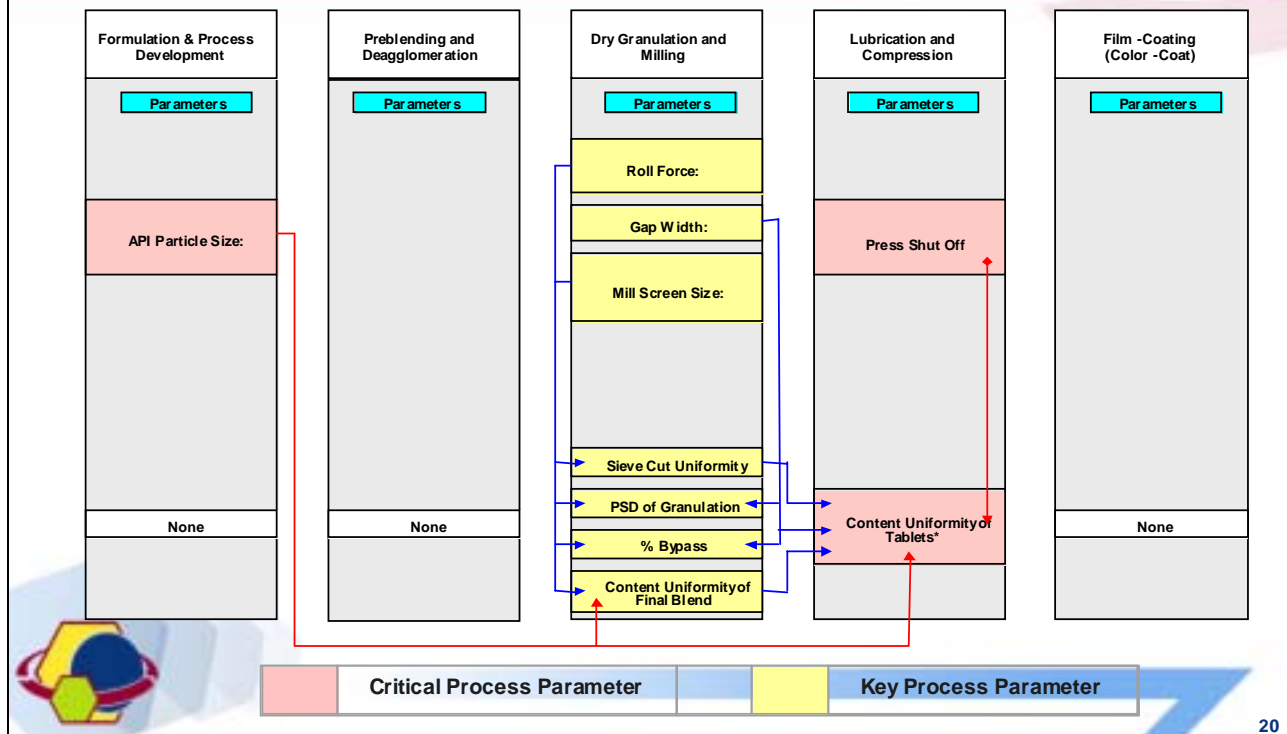
Compression: Identifying “Edge of Failure” for Content Uniformity



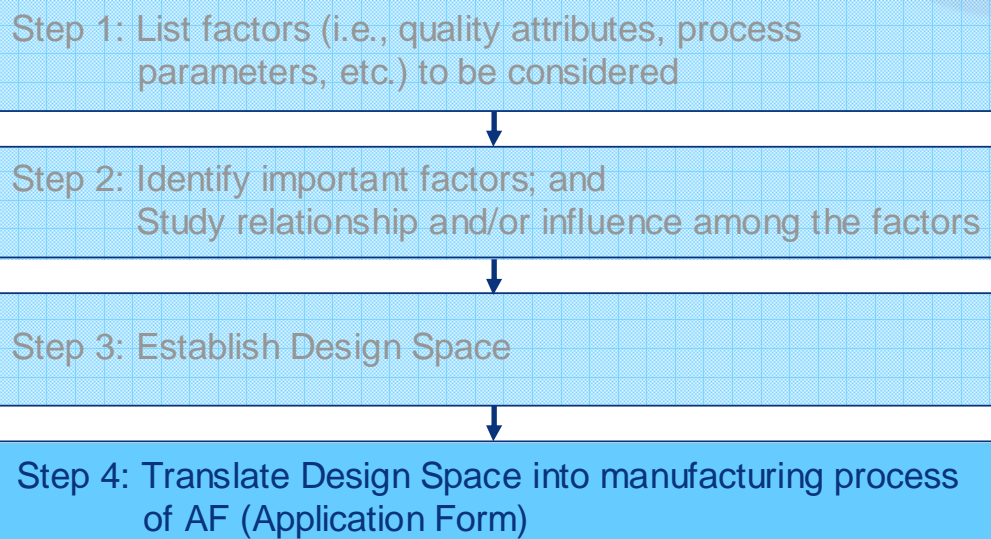
Summary of Compression/Content Uniformity Study

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 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



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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



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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



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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



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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



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- | | |
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