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.

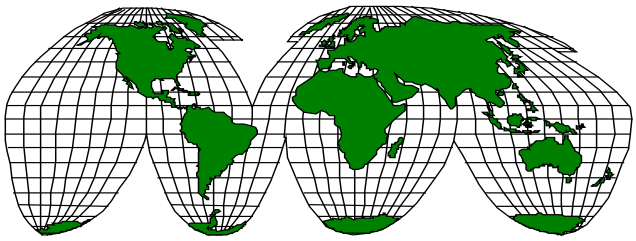
ISPE Facts (ISPEとは)

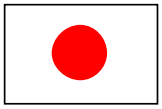
- Founded in 1980 （1980年に創立)
- Not-for-profit （非営利団体)
- More than 23,000 Members in 81 countries
  （81カ国2万3千人以上の会員から成り立っている)
- Focused on education, information exchange, and technical documents for Industry
  （製薬産業向けの専門技術教育、情報交換ならびに関連技術書の作成を活動の基幹にしている)
- Excellent relationship with regulators globally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

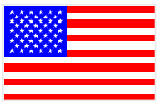
ISPE Affiliates Worldwide (ISPEは世界中に活動を拡大しております)

- 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







ISPE

ICH Q8 Update

Fritz Erni
EFPIA

9.6.2006
PQF/ISPE

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

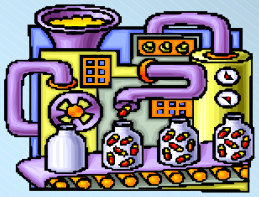
What is ICH Q8!

- 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

ICH Q8

Door opener for Quality by Design



- Is Part of the New ICH Q's (Q8,Q9,Q10)

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

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

Where to put information in on :

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

When to update the document

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

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

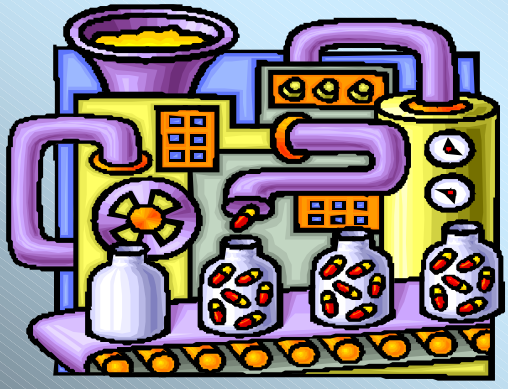
The Pharmaceutical Development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors.

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!



Q8 – Strategic Questions :

What is the Design Space?

Will be the Base for Continuous Improvement!

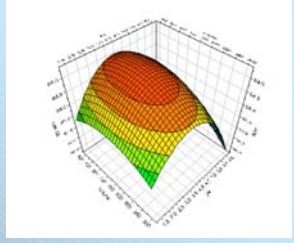
Design Space

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.

Fritz Erni

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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- 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

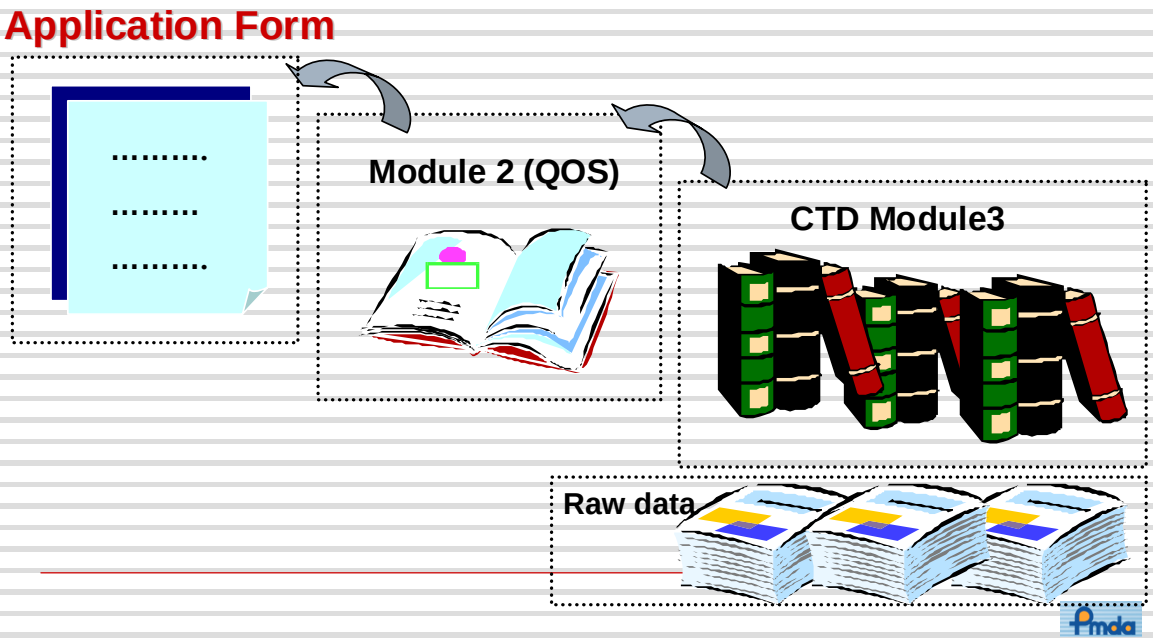
- Japanese CMC Review and Approval system
- Reviewer's views for Design Space
- Future perspective

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 -



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

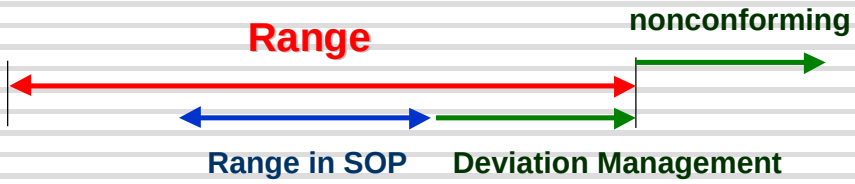
- “Minor Change” system -

- Post-approval Change to Approval matter
  - Partial Change
    - prior-approval change submission
  - Minor Change
    - Notification within 30days of change
    - Data held at site

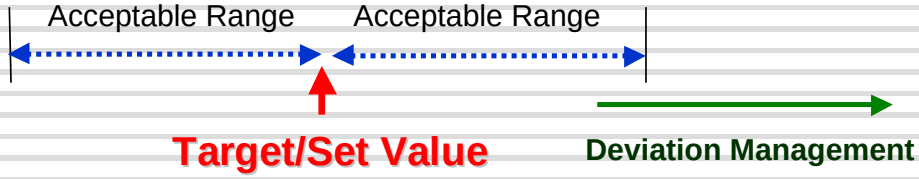
J-NDA Application Form

- Process parameters -

①Range



②Target/Set Value



Reviewer's view for Design Space

- Design Space
- Design Space and "Minor Change" System

Design Space

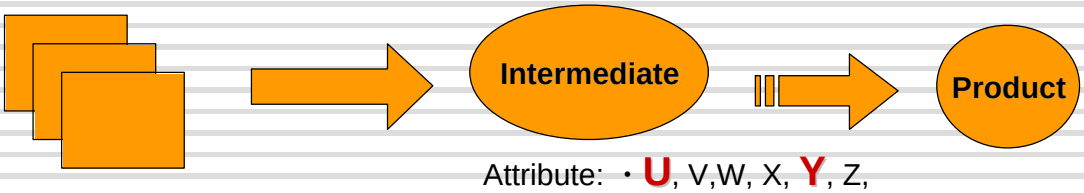
- The **multidimensional combination and interaction** of material attributes and process parameters that have been demonstrated to provide assurance of quality.
- Working **within** the design space is **not** considered as **a change**.
- Movement **out** of the design space is considered to be **a 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 -

Parameter: a_1,b_1,c_1, d_1
Rate; Time; Temp. ;
Power Consumption; et.

Parameter a_2, b_2 ,c_2, d_2
Rate; Time; Temp. ;
Power Consumption; et.

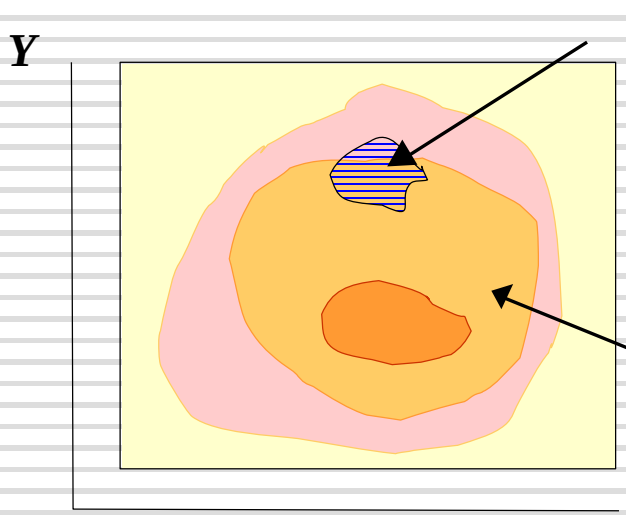


Attribute: ・U, V,W, X, Y, Z,

INPUT 1,2,3
Attribute: A, B, C, D,
・ ・ ・

Process parameters	a1, d1, b2, c2
Material Attribute	U, Y

Design Space



Traditional Process

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

Design Space

- Movement in the design space is not a change

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-	☐Formulation composition ☐etc…	☐Nothing?
Post Approval Change	**Movement** ☐Within not a change? ☐Outside Minor/Partial Change	**Movement** ☐Within not a change ☐Outside a change
Deviation	☐Deviation management in GMP	☐**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

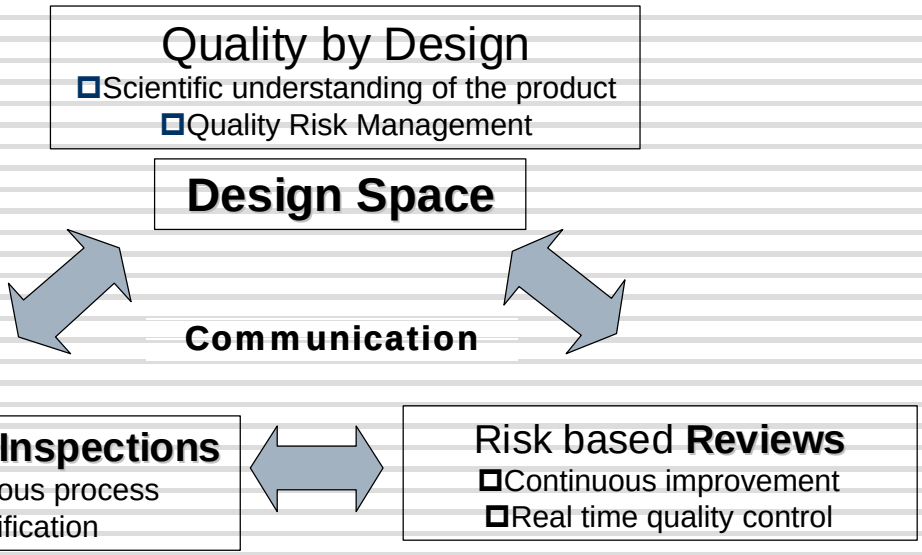
- Primary Review Document and Approval Matters -

- 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

Overview of the Presentation

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

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	

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
- …

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

The “Two Tiered System”

Clear distinction between “baseline expectations” and “opportunities”

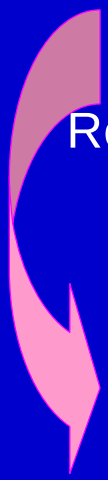
It is entirely the applicant’s decision how much resources to invest and at which time in a product’s life-cycle!

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.

EU: Baseline Expectations



Requirements as outlined in the present

CPMP/QWP Note for Guidance on Development Pharmaceutics

to be met in general

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

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

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

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….

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."

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??

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

What can Design Space be?

- selected aspects, e.g. different sources for one excipient, robustness assessment of selected process parameters

  => baseline approach, limited flexibility

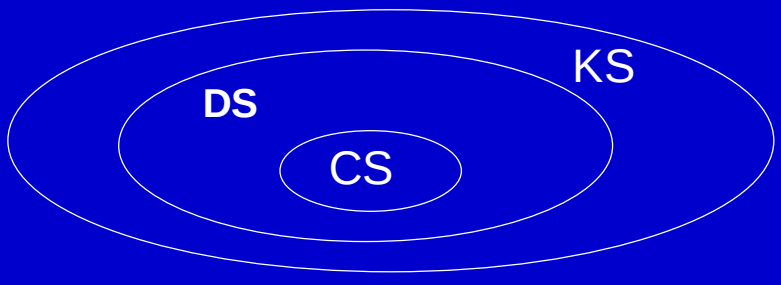
How can Design Space be Achieved?

Formal pharmaceutical development studies
vs.

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

It is up to the applicant/MAH to decide!

Control-, Design- and Knowledge Space



CS: Control space

DS : Design space

KS: Knowledge space

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 staring 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

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.

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

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 ?
    - ……

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

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.

Conclusion

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