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Quality by Design

Correct definition of QbD and its relation to product and process development

MedTechWorld MEDTEC UK

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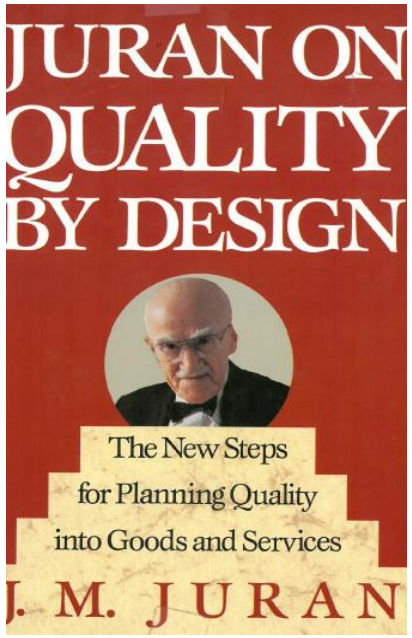
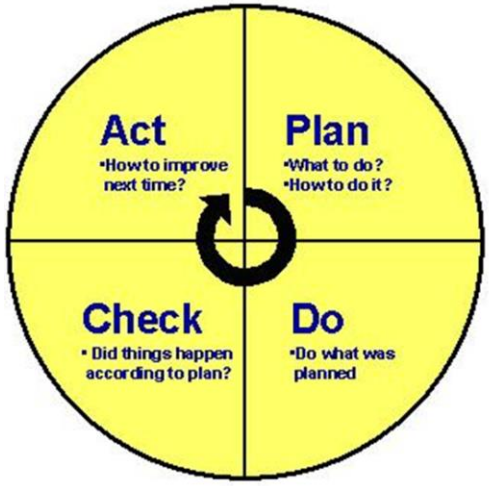
Agenda

- Introduction
- Some history and scene setting
- Relationship of QbD to ICH guidelines
- Overview and definition of QbD
- Relationship to MedTech design process
- Design space
- Control strategy



Quality by Design – coined by J M Juran (1904-2008) - pioneer and evangelist for quality management techniques.

The Juran Trilogy
- Quality Planning
- Quality Control
- Quality Improvement

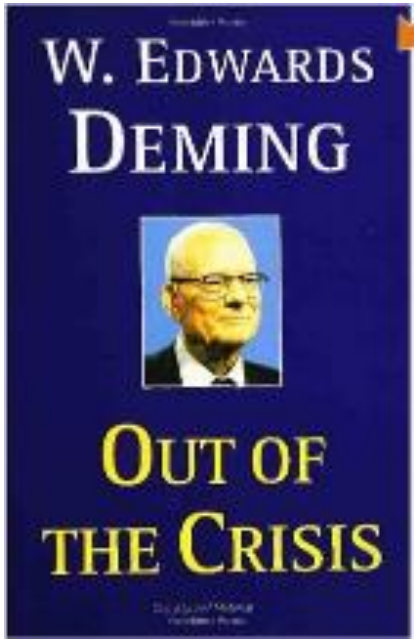


Statistical approach owes more to W Edwards Deming (and others)

"Cease dependence on inspection to achieve quality. Build quality into the product in the first place."

"There is no substitute for knowledge."

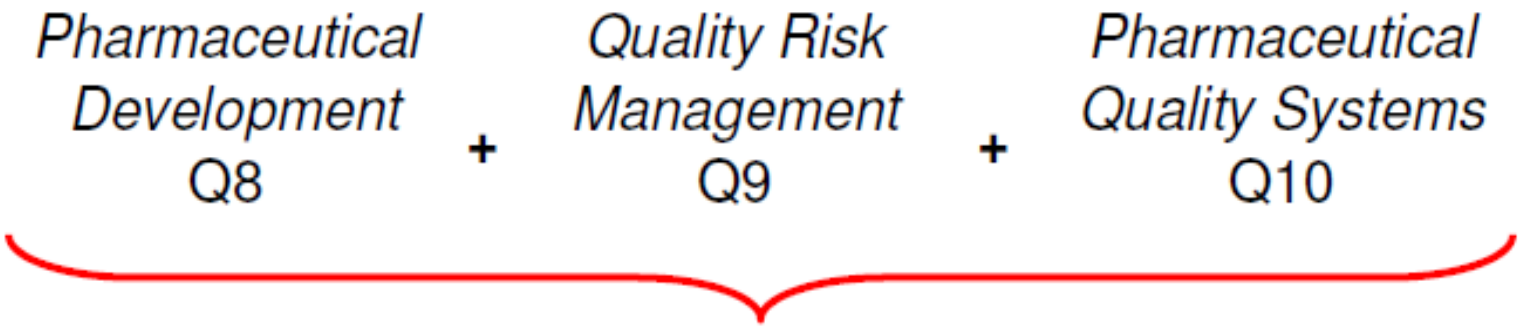
"Experience by itself teaches nothing."



- QbD techniques were adopted in many industries from 1970's onwards, particularly automotive and electronics.
- Quality planning principles are enshrined in the ISO9001 and ISO13485 for design and manufacturing processes.
- Recent usage of the term stems from adoption by FDA for modernisation of review and approval process for pharmaceutical and biotechnology products.
- ICH*– developed a new set of guidelines for pharmaceutical development

*ICH = International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

The ICH Vision as Described in Guidelines

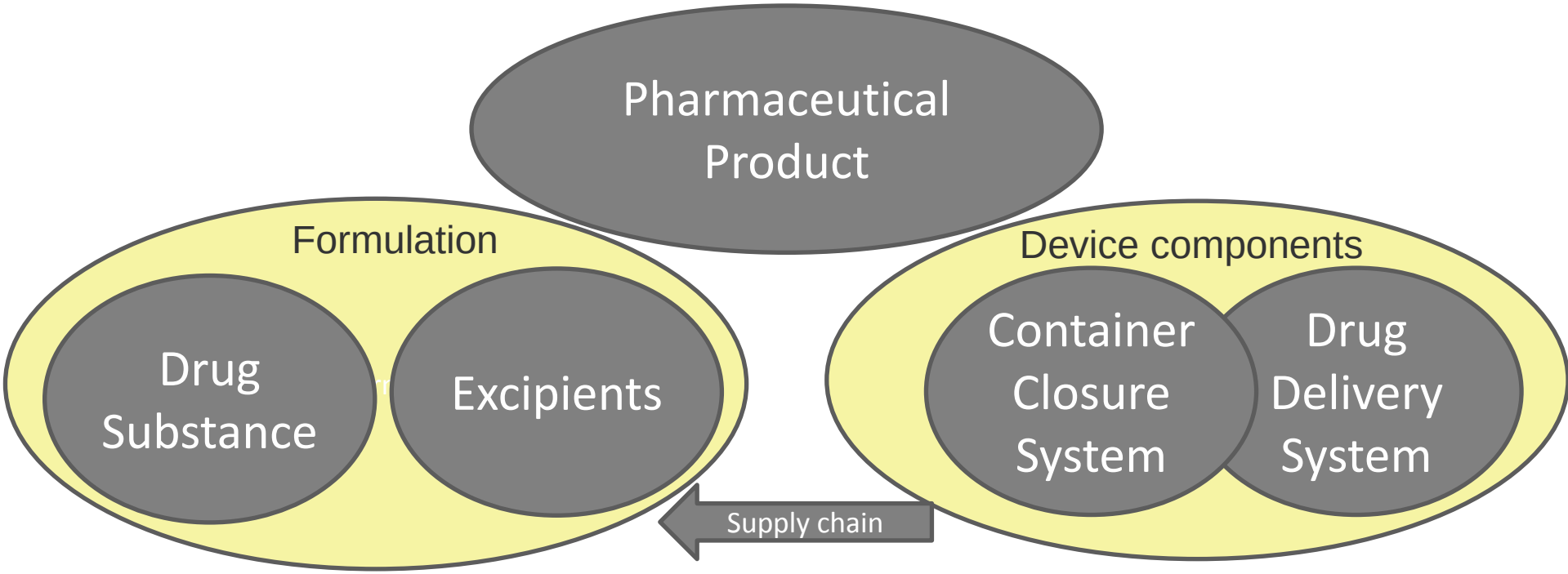


A New Quality Paradigm

- Science and risk-based approaches to pharmaceutical product development, dossier submission, review, inspection and post-approval change management
- Manufacturers empowered to effect continuous improvement and technical innovation throughout the product lifecycle
- Efficient and consistent regulatory oversight across/between regions

Q. Where should QbD be applied?

A. To all elements of a drug or biotechnology product



ICH Guideline Q8 defines QbD as…

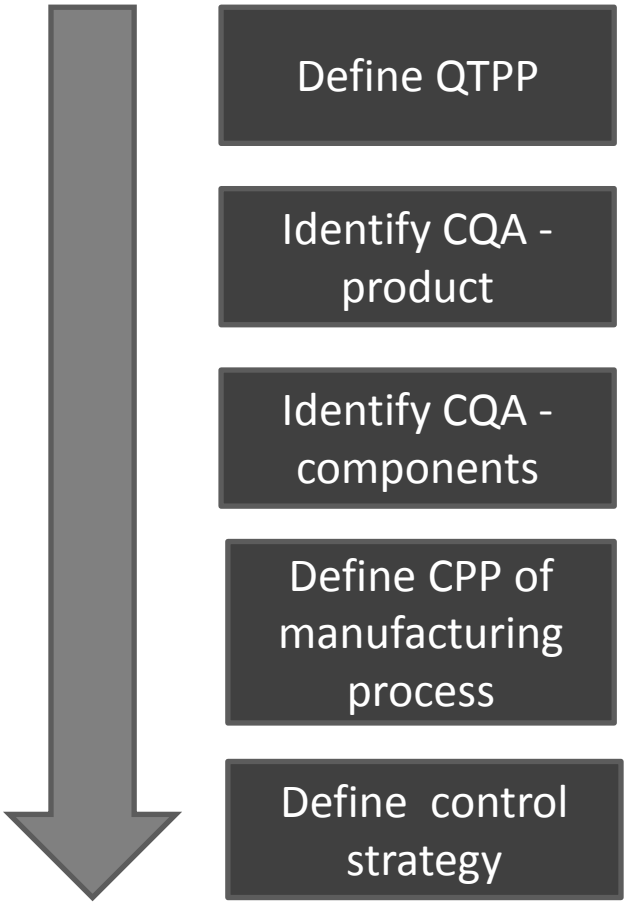
A systematic approach to development
that begins with predefined objectives &
emphasizes product and process understanding and process control, based on sound science &
quality risk management

..and Quality as the degree to which properties of a product, system or process fulfil requirements

Quality by Design is….

- A scientific, risk based proactive approach to pharmaceutical product development
- A deliberate and structured design effort from first stages of conception and innovation through the full product life cycle
- A complete understanding of how product attributes and process parameters relate to product performance.

General approach



Quality Target Product Profile
- Use and market related target requirements
- Related to safety and efficacy
- Intended use, dosage form, dosage strength
- Quality criteria - sterility, purity, stability, etc.

Critical Quality Attribute
- Physical, chemical, biological property
- Should be within a defined range to ensure product quality
- Related to materials, intermediates, final product.

Critical Process Parameter
- Parameter whose variability has an impact on a CQA
- Should therefore be monitored or controlled

Minimalist approach

Quality target product profile

Define QTPP

Critical quality attributes

Identify CQA - product

Identify CQA - components

Critical process parameters

Define CPP of manufacturing process

Define control strategy

"Quality by Design"

Systematically understand and refine the product and process

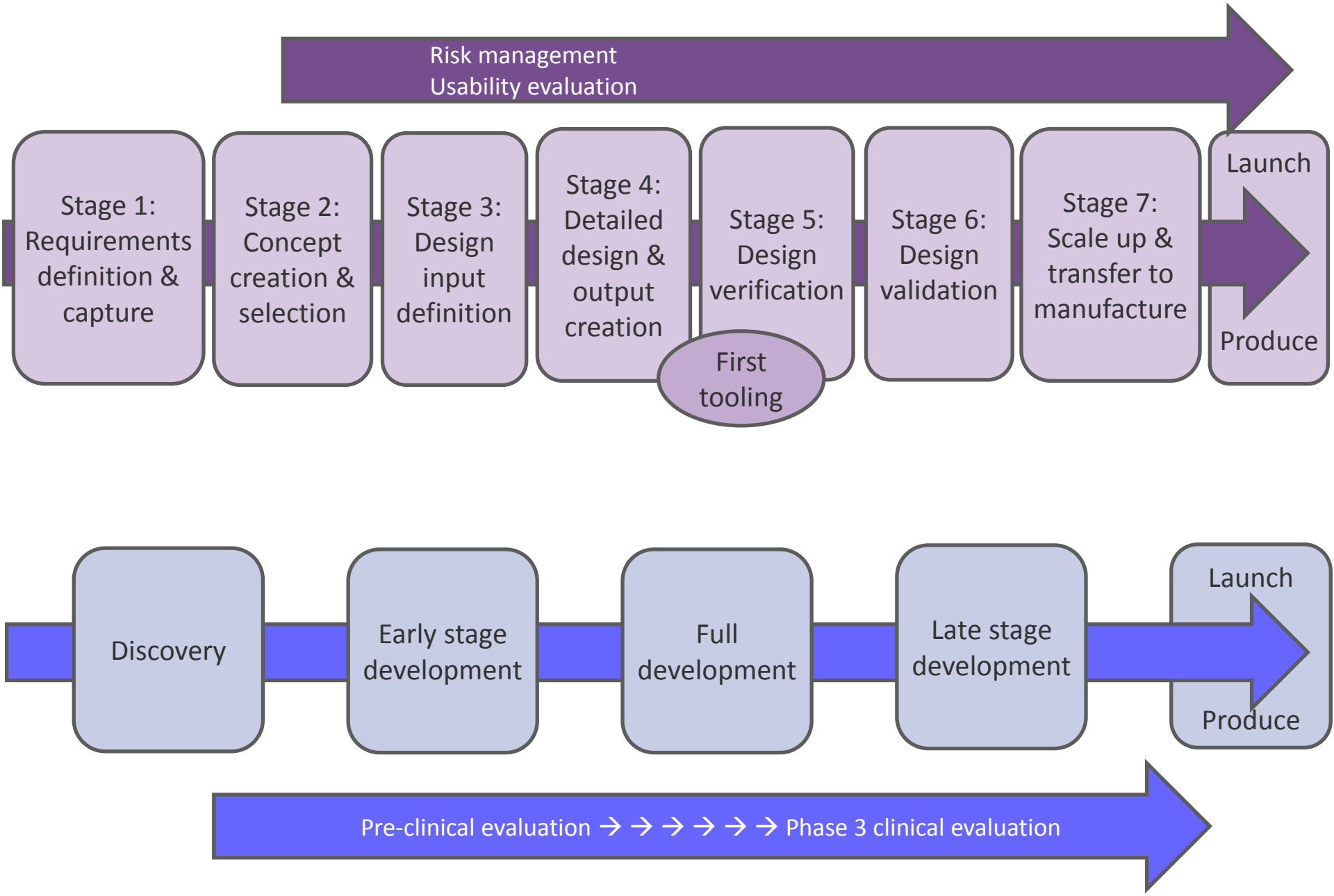
Risk assessment
Knowledge
Experiment

Identify material attributes and process parameters that affect CQAs and the functional relationships between them

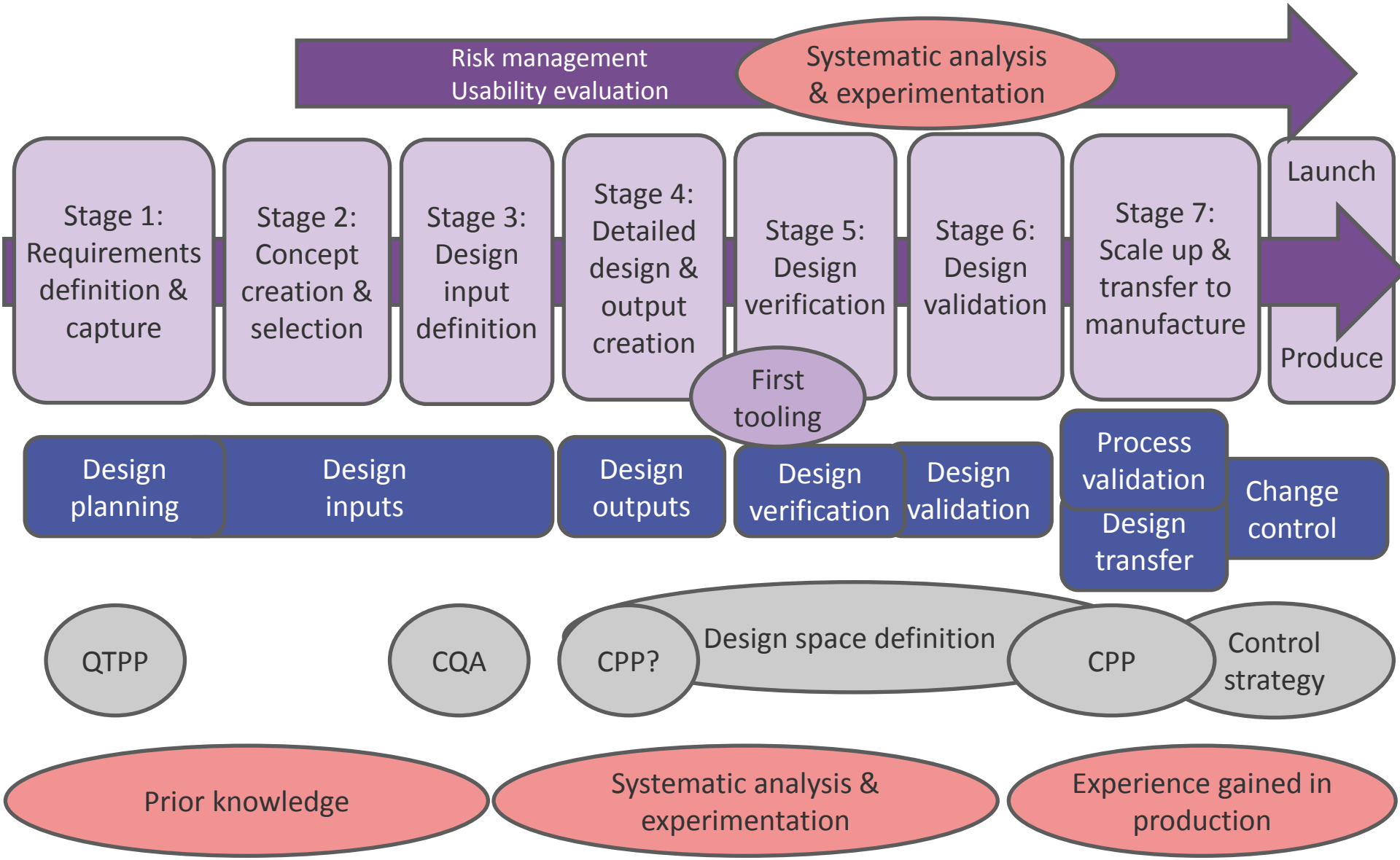
Establish control strategy
e.g. design space
e.g. real-time release testing

Continual improvement
Reduced variability
Innovation

Stage-gated device design processes



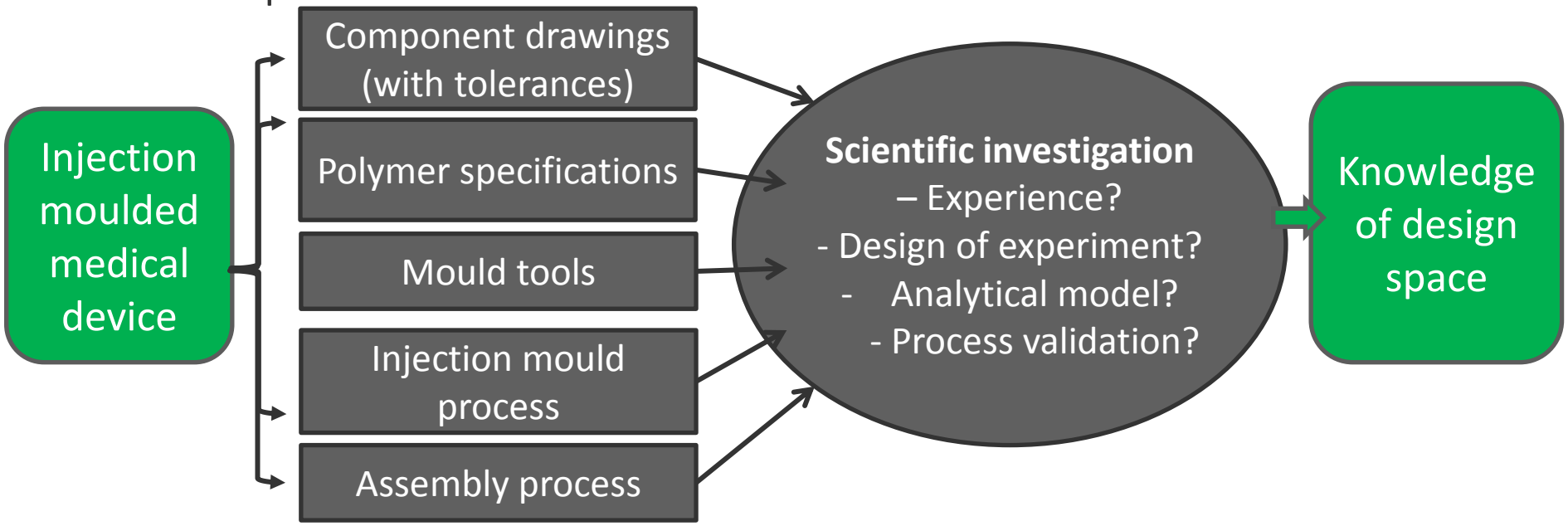
Medical device stage gated device design process



ICH 8 defines design space as:

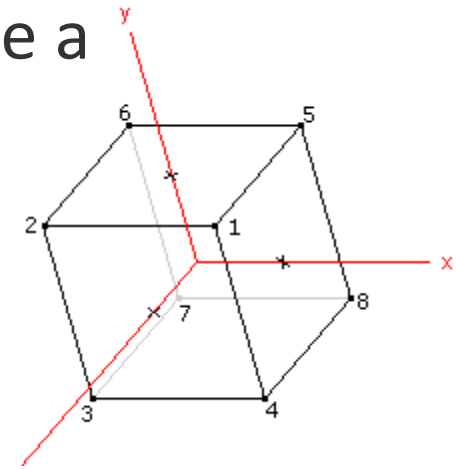
The multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality.

For example:



2D component drawings generally define a tolerance for each dimension

- X = 30 +/- 0.2 mm
- Y = 0.5 +/- 0.05 mm
- θ = 15 +/- 0.5°, etc.

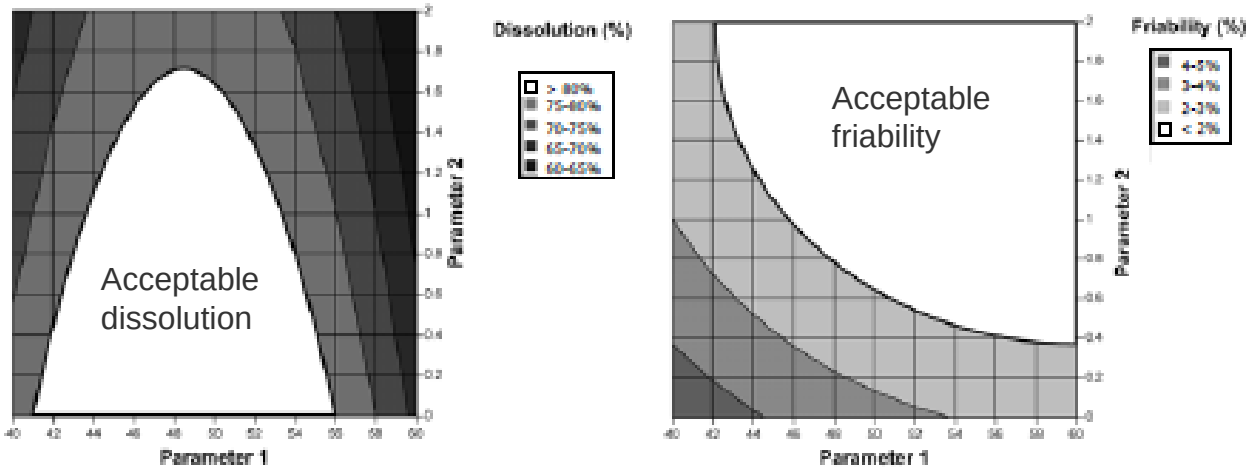


… which define a multi-dimensional space within which the product will **always work** (worst case analysis)

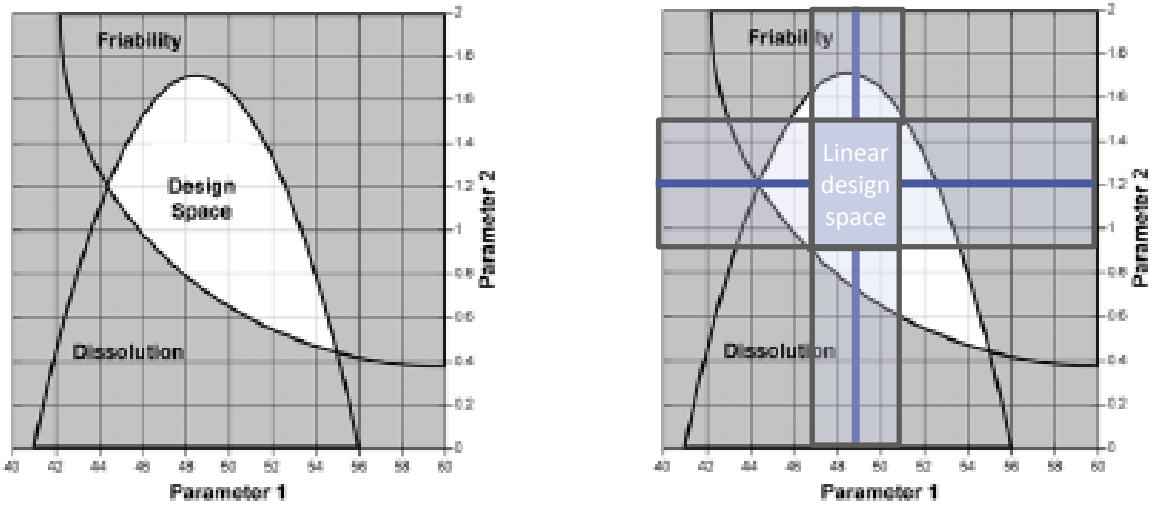
or **probably work** (statistical analysis) work.

In many cases it may be preferable to define the design space in terms of proven functional relationships between the different factors.

Advantages of non-linear design space



Effects of 2 processing parameters in a tableting operation



Source: ICH Topic Q8 (R2)

Comments on Design Space

- Can a Design Space ever be complete?

  - Yes, if all parameters with a potential effect are investigated in all combinations. In other words – Not really.

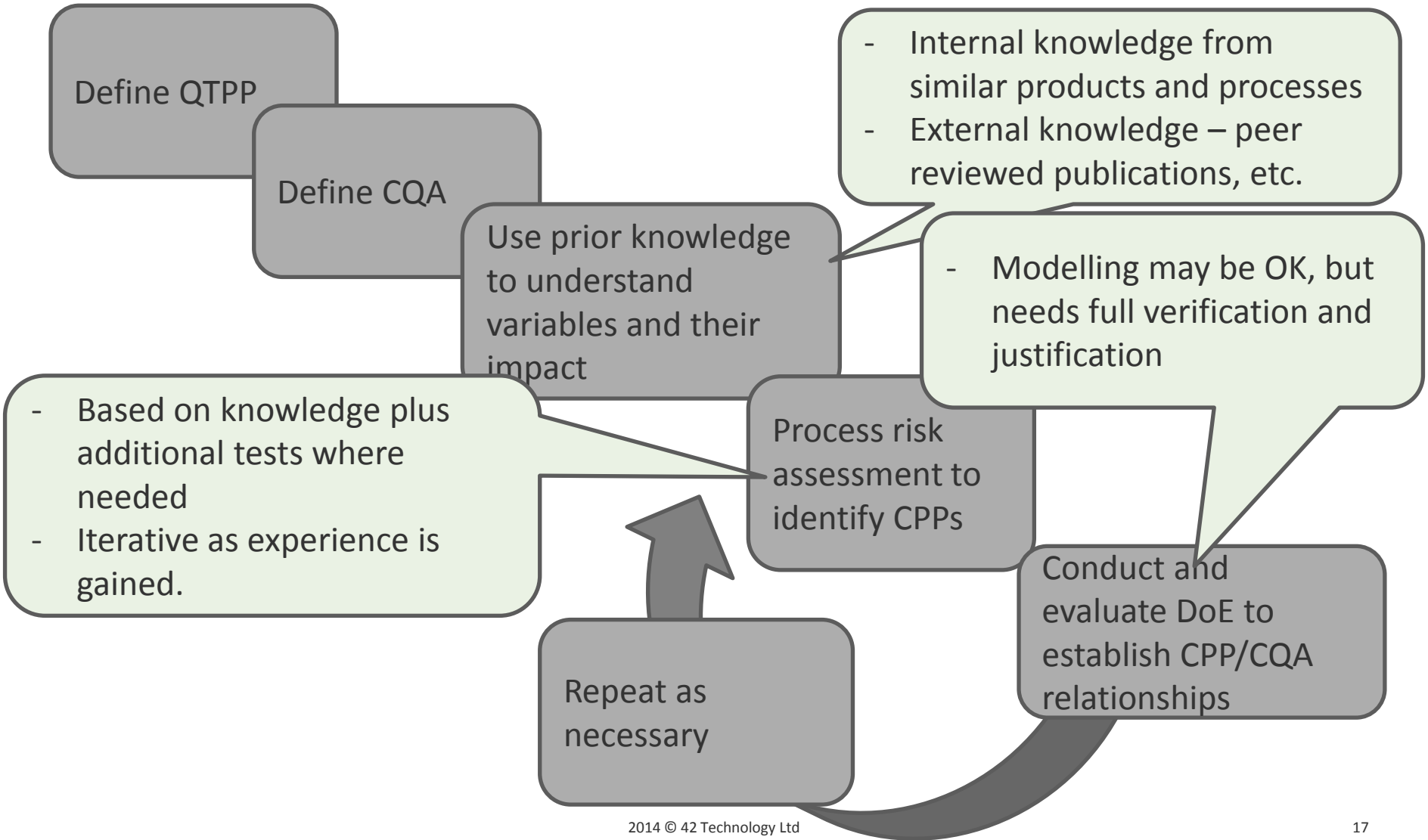
  - Risk management is needed to ensure itsrobustness of the Design Space

- Design Space does not need to go to the edge of failure
  – useful to know, but not mandatory

- Set of proven acceptable ranges is not a Design Space

- Design space should be verified at each scale of manufacture.

Steps in development of a process Design Space



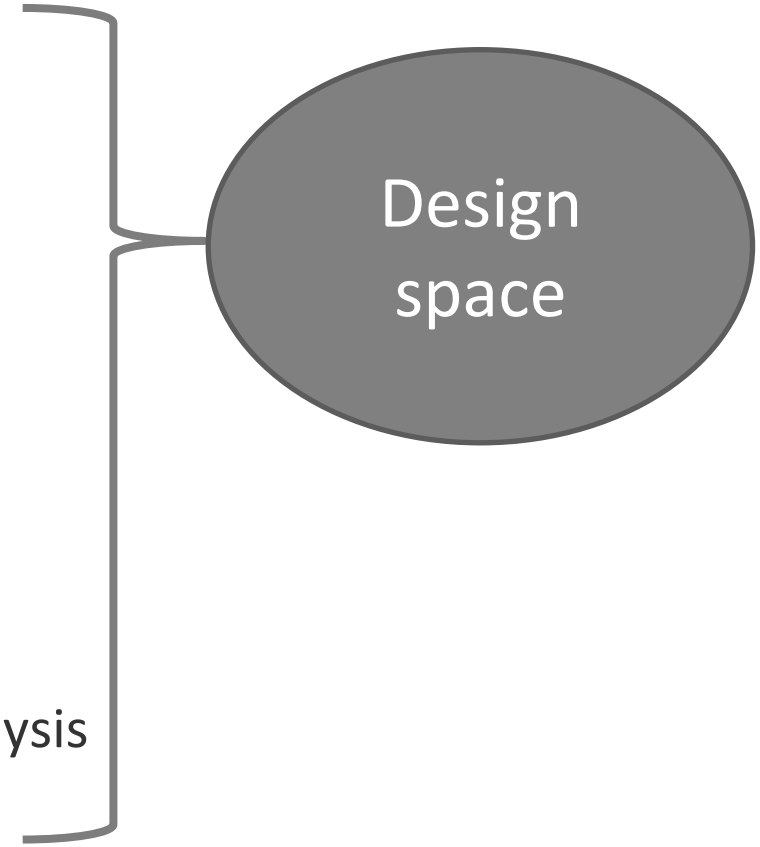
Can we analyse the relative contributions of the identified CPP and CQA to variability or failure of the device?

Theoretical

- Tolerance analysis
- Sensitivity analysis
- Theoretical modelling of mechanisms
- Finite element analysis

Experimental

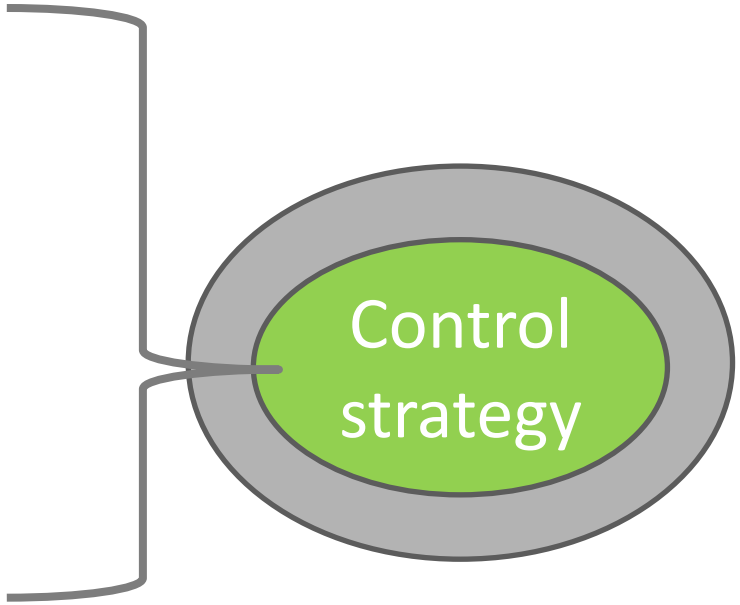
- Single factor experiments
- Designed experiments for multi-factor analysis
- Validation/ verification studies



Control strategy

Needs to ensure that required quality is produced consistently and is assured by combination of:

- In-process control and measurements
- Upstream process controls
- Input material controls



Must be based on understanding of CPPs and the impact of variability.

Can enable adaptive process steps that vary according to input materials.

Can ultimately lead to real time release testing.

Summary

- QbD is recommended for 21st century pharmaceutical development – and by extension to Container Closure Systems
- QbD has less impact on MedTech product development processes since the requirements are close to good design and manufacturing practices.
- QbD requires profound understanding of effects of, and interactions between, materials, products and process parameters.
- QbD leads to a more flexible manufacturing environment, responsive to upstream variability
- CCS and drug delivery system component suppliers need to prepare to share information with pharmaceutical clients.

Thank you for you attention.

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