QUALITY BY DESIGN, DESIGN OF EXPERIMENTS, PROCESS ANALYTICAL TECHNOLOGY

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QUALITY BY DESIGN AND DESIGN OF EXPERIMENTS CONCEPT

Definition of Quality by Design:

- Systematic approach to development and manufacturing;
- The concept of QbD is to determine the critical quality attributes of a product resulting in a target product profile;
- Begins with predefined objectives;
- Emphasizes product and process understanding and process control;
- Based on sound science and quality risk management.

QUALITY BY DESIGN AND DESIGN OF EXPERIMENTS CONCEPT

Definition of Design of Experiment:

- Strategy to gather empirical knowledge, i.e. knowledge based on **the analysis of experimental data** and not on theoretical models. It can be applied when investigating a phenomenon in order to gain understanding or improve performance.

QUALITY BY DESIGN AND DESIGN OF EXPERIMENTS CONCEPT

Approach to Process Validation (FDA Guideline excerpt):

Stage 1 – Process Design
The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities;
Stage 2 – Process Qualification
During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing;
Stage 3 – Continued Process Verification
Ongoing assurance is gained during routine production that the process remains in a state of control.

Quality by Design and Design of Experiments Concept

QbD = Process Understanding

A process is considered well understood from the physico-chemical perspective when

- All key (critical) sources of variability are explained;
- Quality attributes can be **predicted** based on key (critical) inputs;
- Process capability of “Key (Critical) Quality Attributes“ meets acceptance levels.

A well understood process is by definition a process with a low risk of delivering of a poor quality product.

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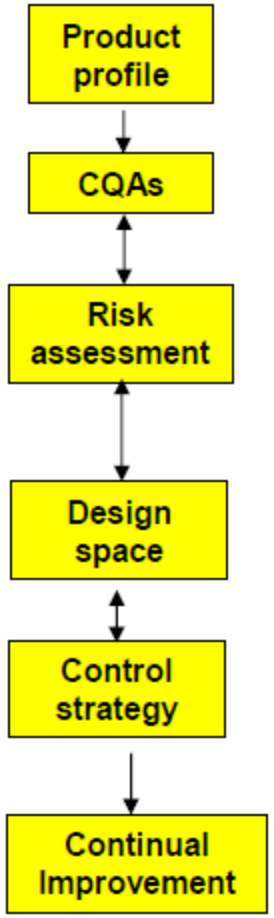

- Target the product profile
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

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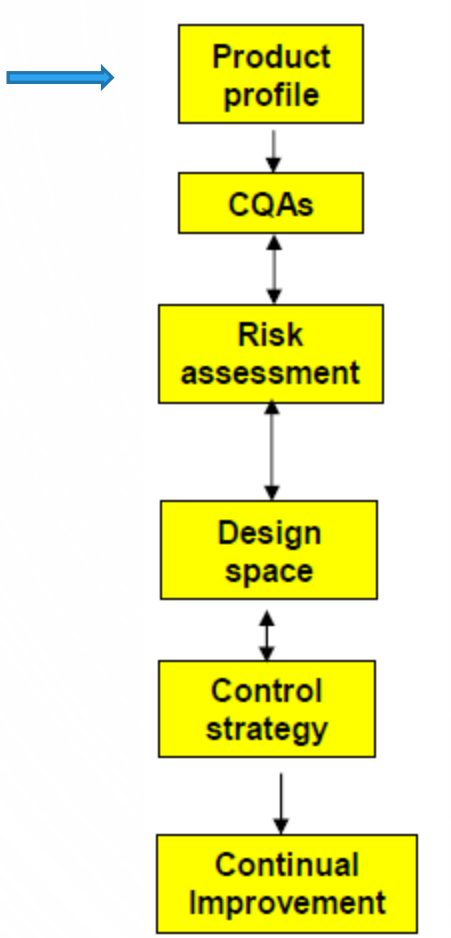

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Target the product profile

I want a flower !

But I wanted something different !!

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Target the product profile

- Dosage Form
- Characteristics – appearance, shape, form, size
- Strength
- Assay
- Purity/impurity
- Stability
- Others
- cQAs

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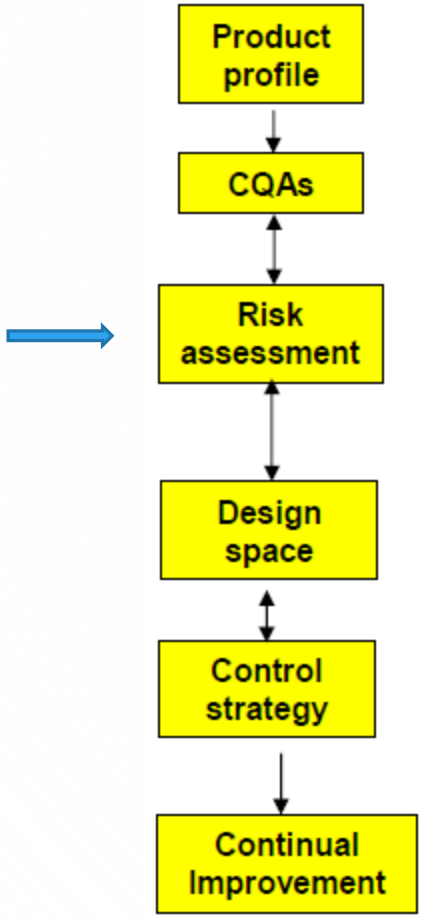

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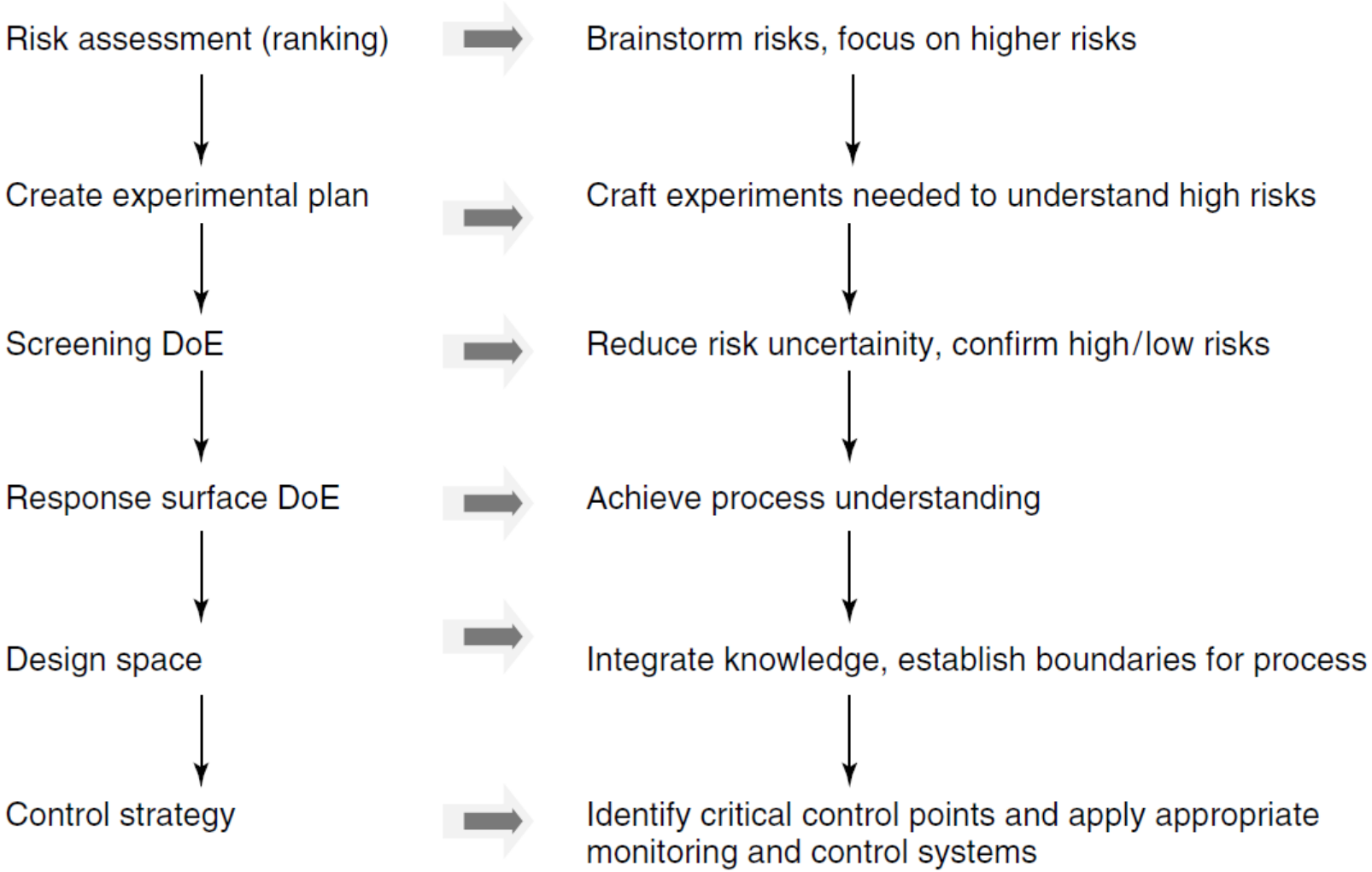

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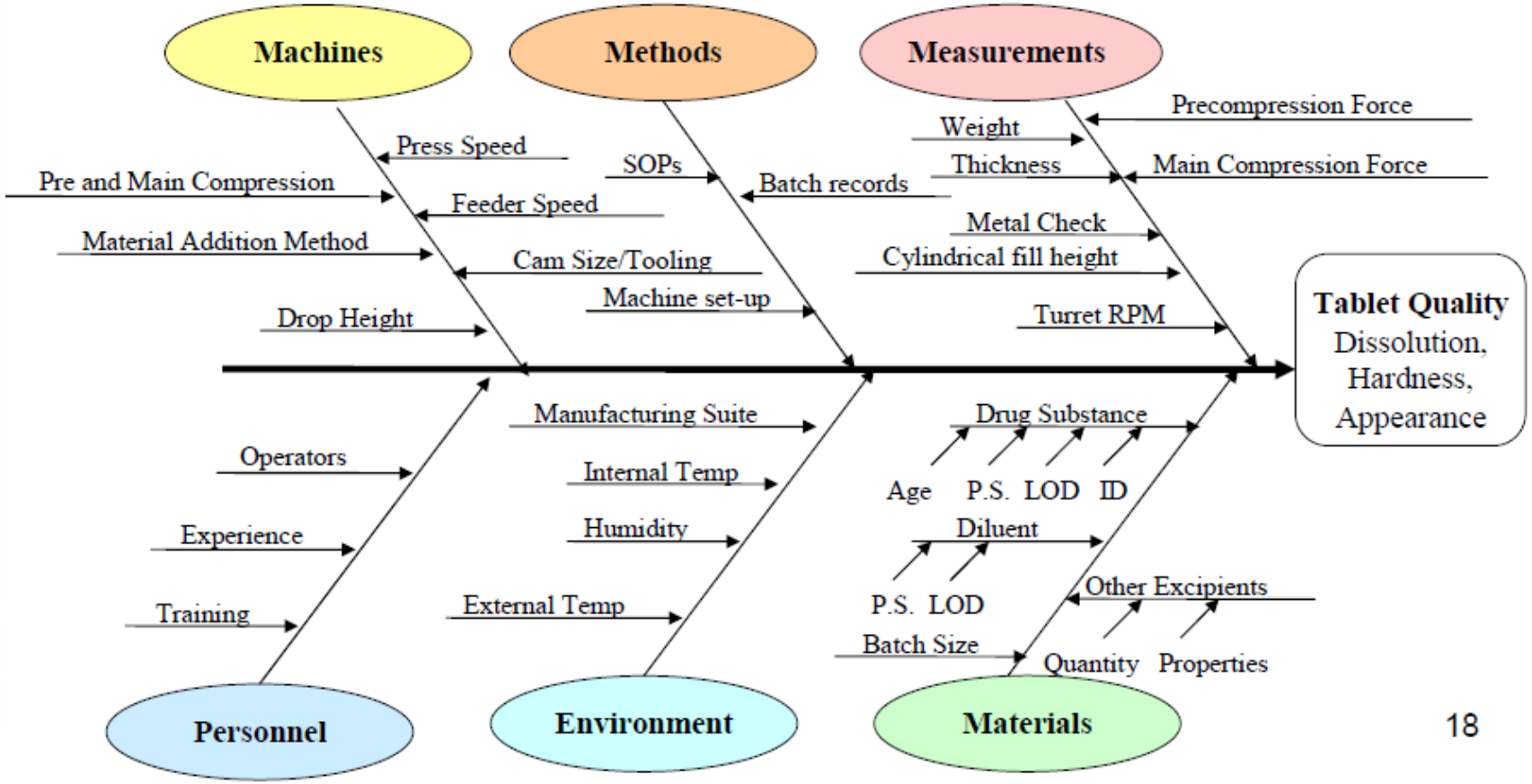
Risk assessment – Ishikawa (fishbone) diagram



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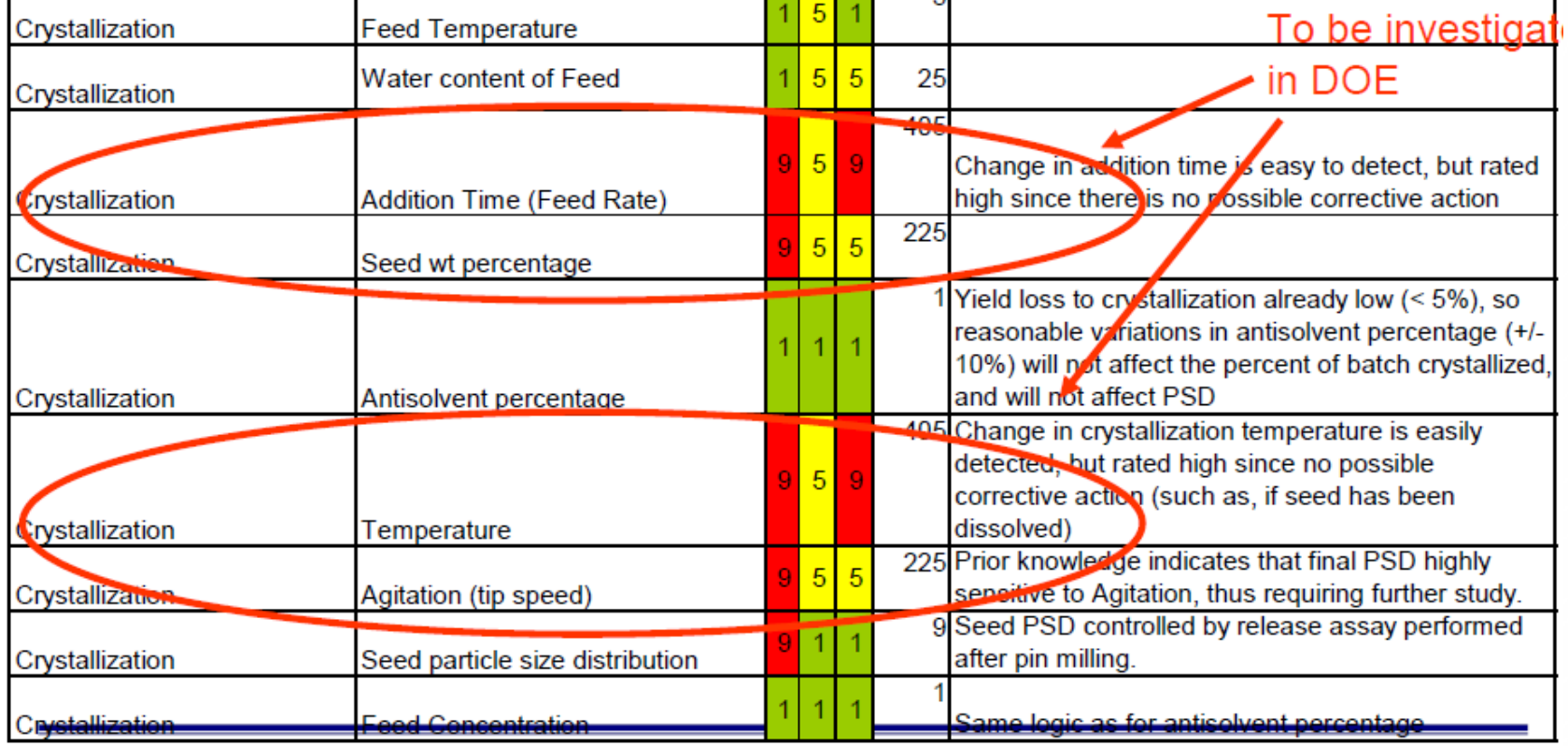
What is the **Impact** that ---------- will have on purity? 1) minimal 5) moderate 9) significant						
What is the **Probability** that variations in ---------- will occur? 1) unlikely 5) moderately likely 9) highly likely						
What is our **Ability to Detect** a meaningful variation in ---------- at a meaningful control point? 1) certain 5) moderate 9) unlikely						
Unit Operation	**Parameter**	**IMPACT**	**PROB.**	**Detect**	**RPN**	**Comments**
Crystallization	Feed Temperature	1	5	1	5	
Crystallization	Water content of Feed	1	5	5	25	
Crystallization	Addition Time (Feed Rate)	9	5	9	405	Change in addition time is easy to detect, but rated high since there is no possible corrective action
Crystallization	Seed wt percentage	9	5	5	225	
Crystallization	Antisolvent percentage	1	1	1	1	Yield loss to crystallization already low (< 5%), so reasonable variations in antisolvent percentage (+/- 10%) will not affect the percent of batch crystallized, and will not affect PSD
Crystallization	Temperature	9	5	9	405	Change in crystallization temperature is easily detected, but rated high since no possible corrective action (such as, if seed has been dissolved)
Crystallization	Agitation (tip speed)	9	5	5	225	Prior knowledge indicates that final PSD highly sensitive to Agitation, thus requiring further study.
Crystallization	Seed particle size distribution	9	1	1	9	Seed PSD controlled by release assay performed after pin milling.
Crystallization	Feed Concentration	1	1	1	1	Same logic as for antisolvent percentage



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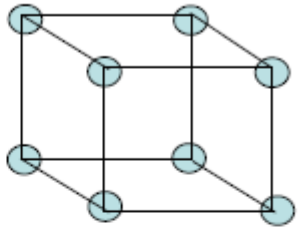
Design of Experiments (DOE): an efficient method to determine relevant parameters and interactions

1. Choose experimental design

(e.g., full factorial, d-optimal)

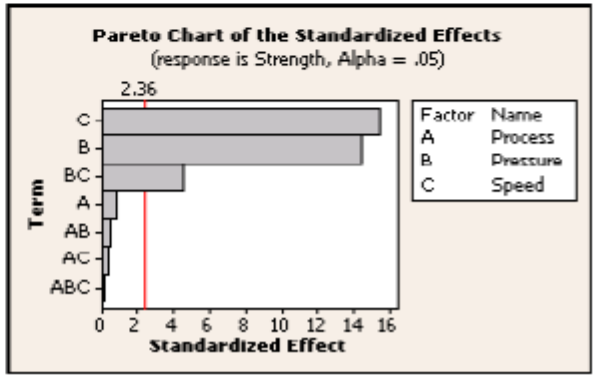


2. Conduct randomized experiments

Experiment	Factor A	Factor B	Factor C
1	+	-	-
2	-	+	-
3	+	+	+
4	+	-	+

3. Analyze Data

Determine significant factors



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- DOE results in **a set of experiments**.
  All factors are varied, **systematically** and **independently**.
  The number and type of factors and regression model specify the prerequisites.
  The DOE defines the optimal number of runs and the best factor combinations for the runs.
  DOE is used for three primary experimental objectives screening:
    which factors are important and what are their appropriate ranges?
    optimization: what are the optimal factor settings?
    robustness testing: how sensitive is a response to small factor changes?
  Advantages with DOE compared to OVAT:

factor interactions are estimable;
reliable maps of the systems;
seen effects and noise are separable and estimable;
probability analysis.

Carlson, R. *Design and Optimization in Organic Synthesis,* Elsevier **1992**

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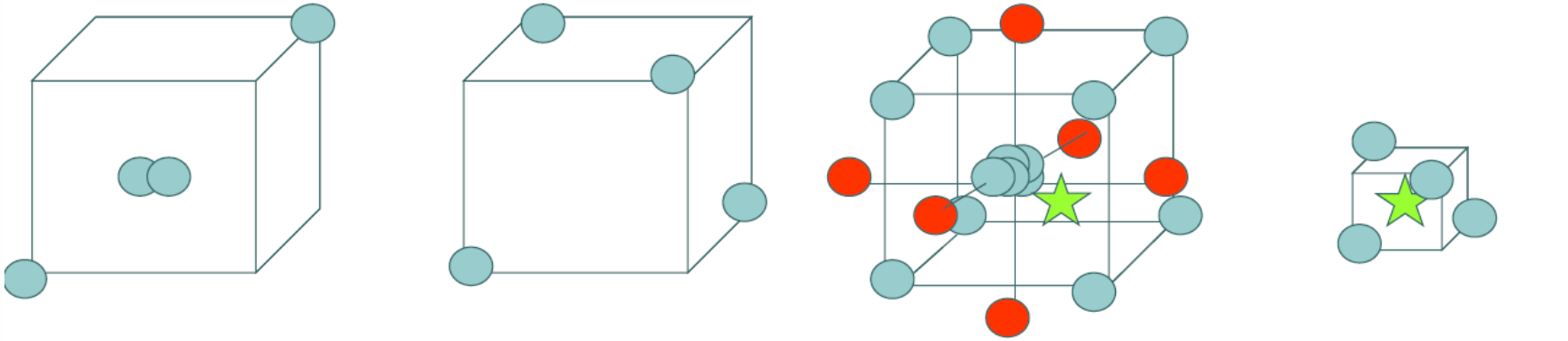

Scoping

Initial assessment

Screening

Fractional designs

Optimizing

Response surfaces

Robustness

Robust designs

Process knowledge

Process Confidence

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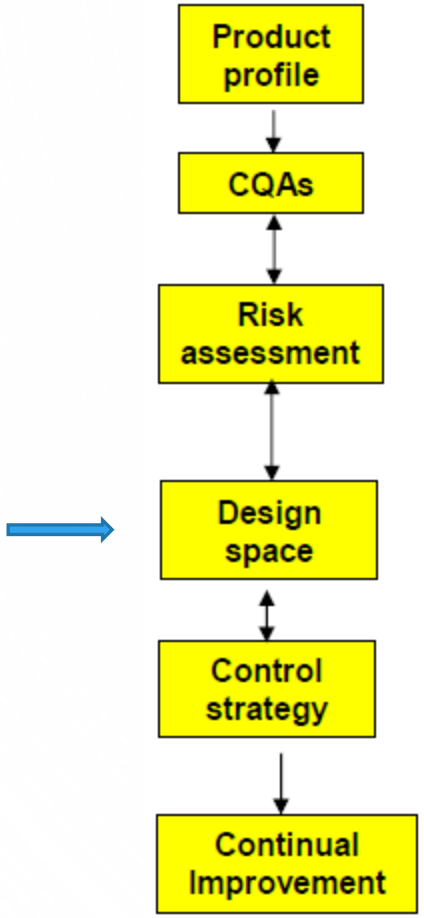

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Design Space

The process design space is a multidimensional combination and interaction of input variables, i.e. material attributes and process parameters, that have been demonstrated to provide adequate quality.

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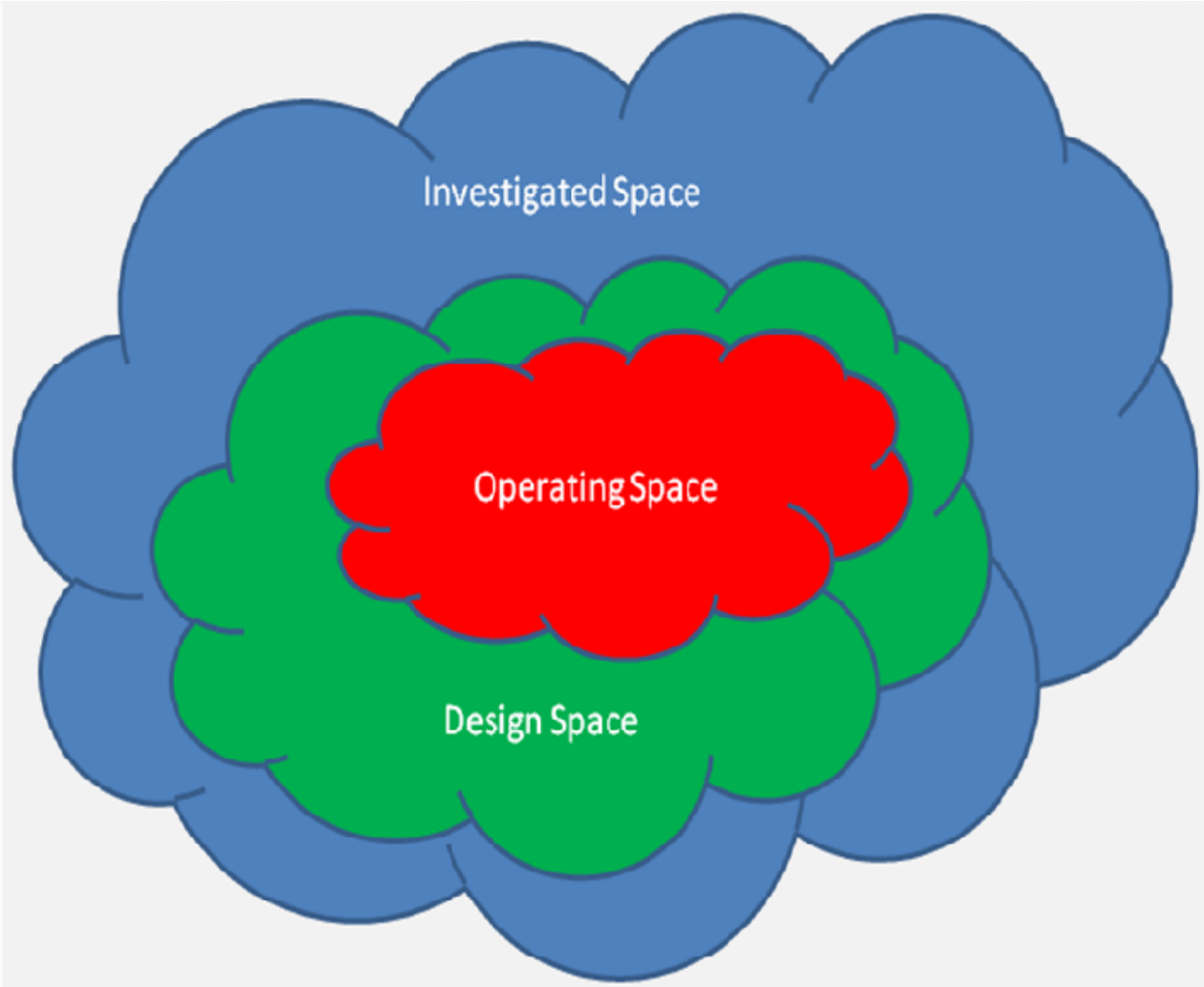

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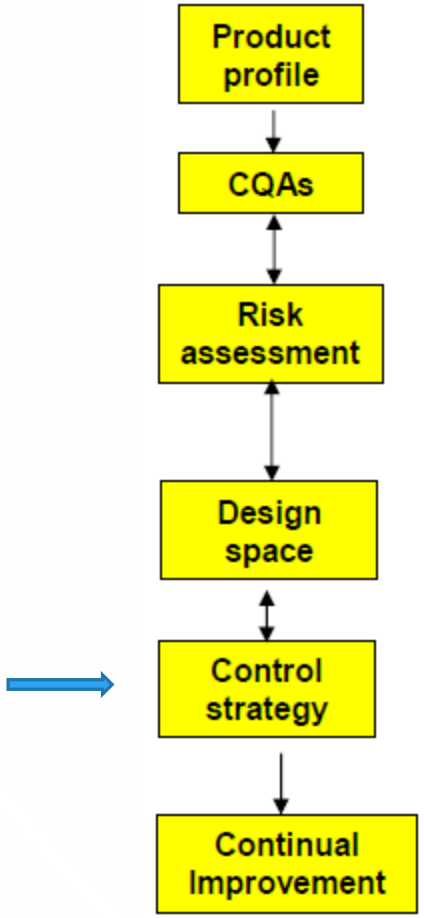

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The Control Strategy must include CQAs and CPPs that are included in the Design Space

Examples:

- Raw material purchase specification
- API characteristics
- Operating ranges for process parameters
- In-process controls
- Acceptance criteria
- Release testing
- API and drug product specifications and their acceptance criteria

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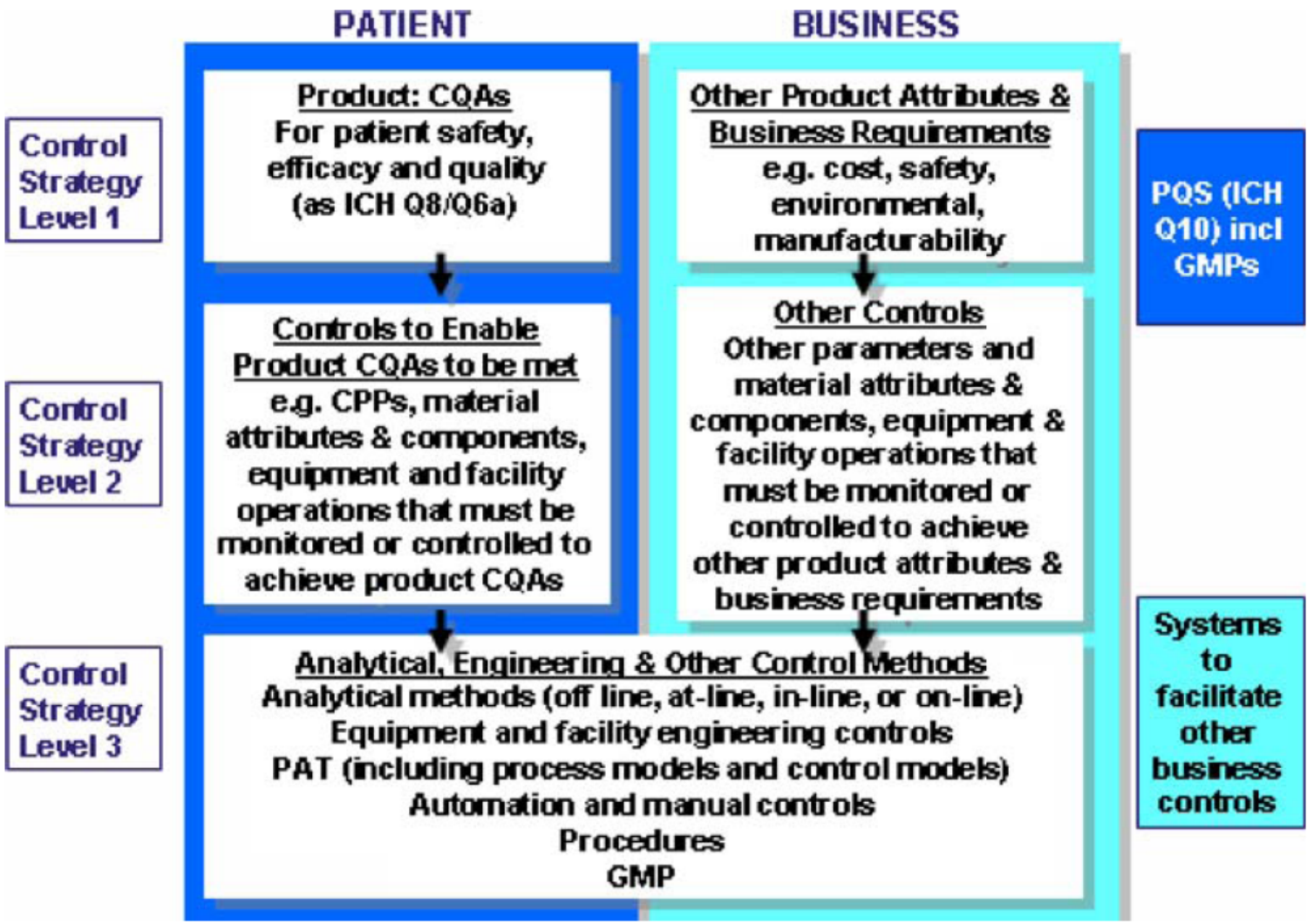

Quality by Design and Design of Experiments
Concept

When fully implemented, QbD means that all critical sources of process variability have been identified, measured and understood so that they can be controlled by the manufacturing process itself. The resulting business benefits are significant:

- Reduced batch failure rates;
- Lower operating cost;
- Increased predictability of manufacturing output and quality;
- Faster tech transfer between development and manufacturing;
- Faster regulatory approval of new product applications and process changes;
- Fewer and shorter regulatory inspections of manufacturing sites;
- Significant reductions in working capital requirements, resource costs and time to value.

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Mohammed, A.Q. *Org.Process Res.Dev. 19*, 1634 (**2015**) – Quality by Design in Action 1

Mohammed, A.Q. *Org.Process Res.Dev. 19*, 1645 (**2015**) – Quality by Design in Action 2

Murray, P.M. *et al Org.Biomol.Chem. 14*, 2373 (**2016**) – the application of design of experiments in reaction optimization and solvent selection