# *"Quality by Design" Application and Perspectives for biologicals*

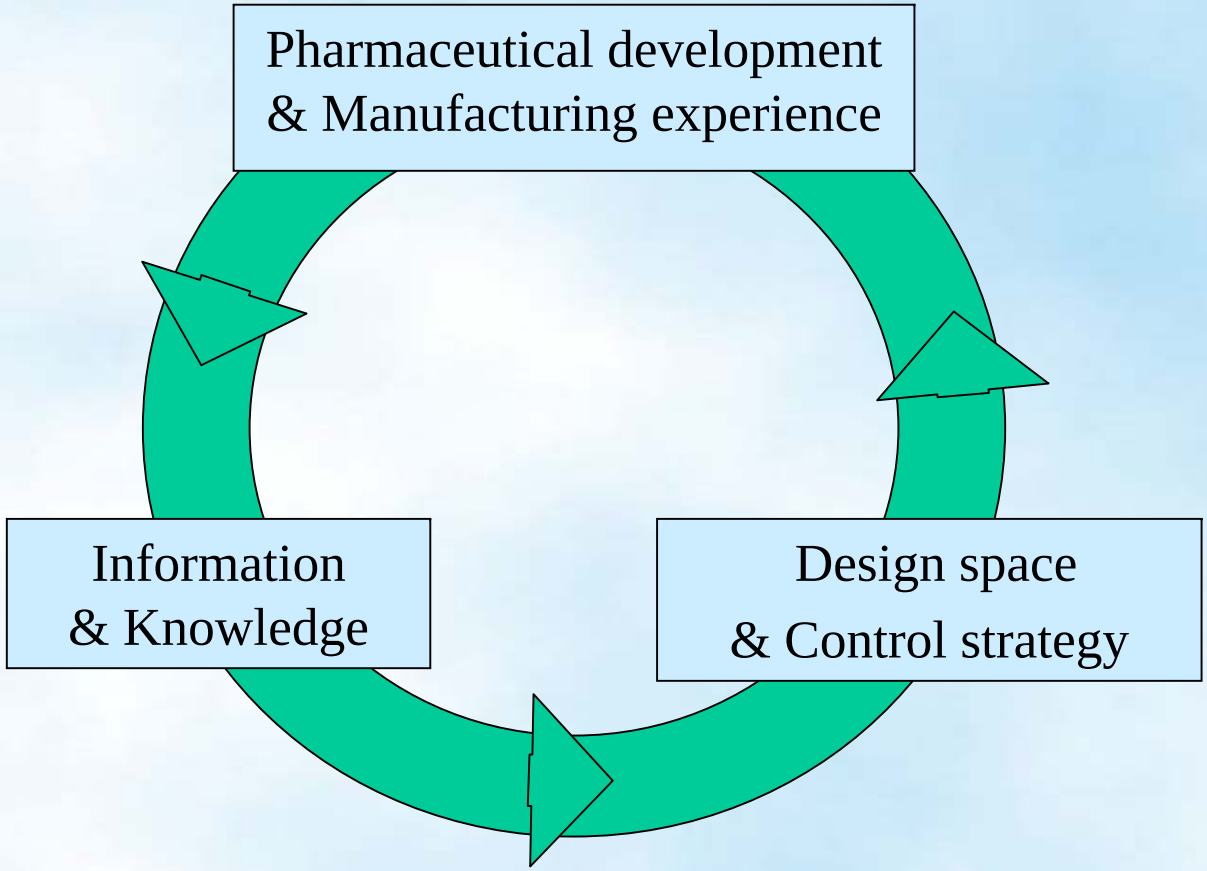
K. Ho, CHMP Biologics Working Party

# Pharmaceutical development (Q8)

Aim:

To design a quality product and a manufacturing process to consistently deliver the intended performance of the product

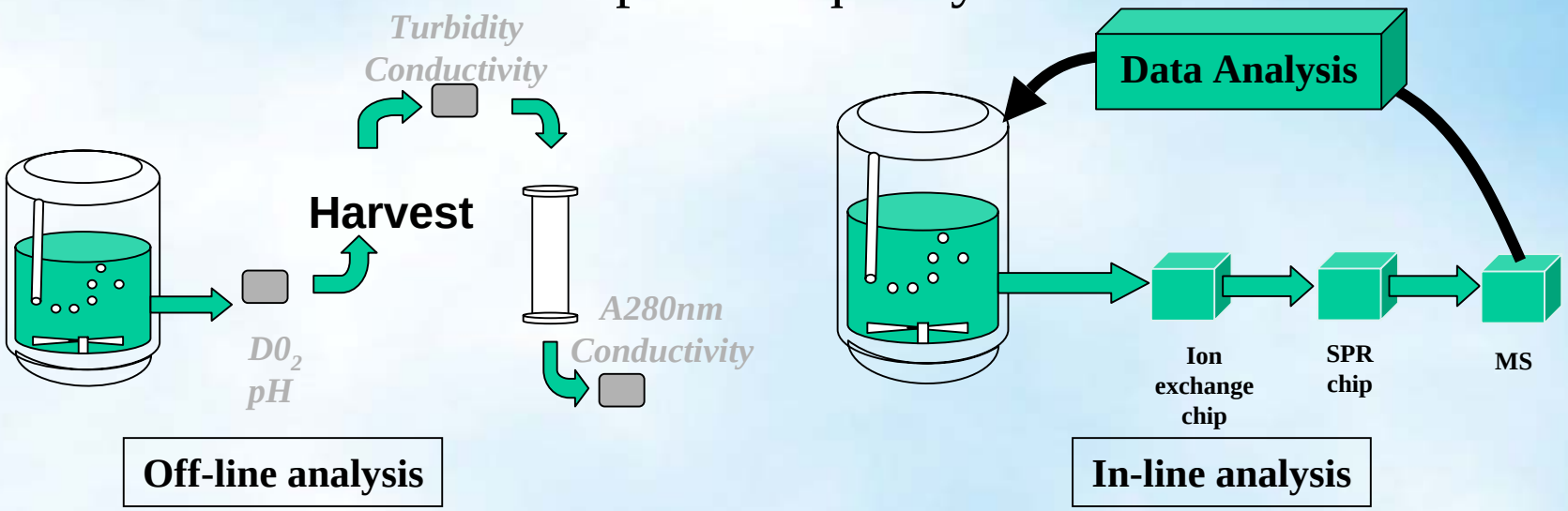
# Pharmaceutical development (Q8)



# Pharmaceutical development tools

**Process analytical technology/PAT:**

a system for designing, analyzing, and controlling manufacturing trough timely measurements of critical quality performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality



# Pharmaceutical development tools

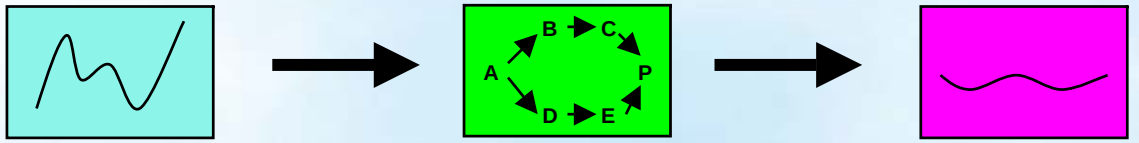
"Traditional" Manufacturing without PAT

**Variable process input** | **„Fixed Process“ (few parameters)** | **Variable Process Output**

Development with PAT

**Variable process input** | **„Process under development“ (many parameters)** | **Optimized Process Output**

Manufacturing with PAT

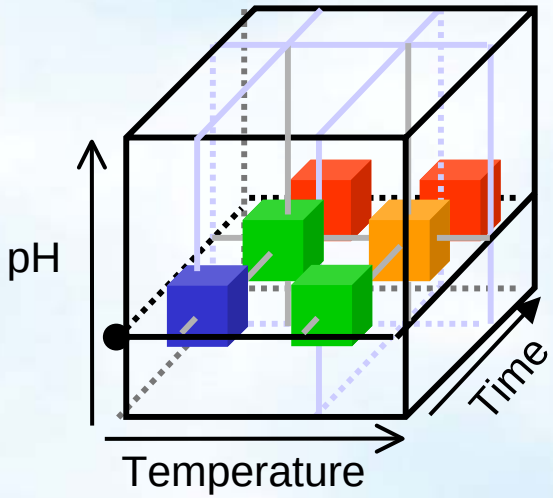



**Variable process input** | **„Fixed Design Space“ = adjustable Process (relevant parameters)** | **Consistent Process Output**

# Pharmaceutical development tools

**Formal experimental design**

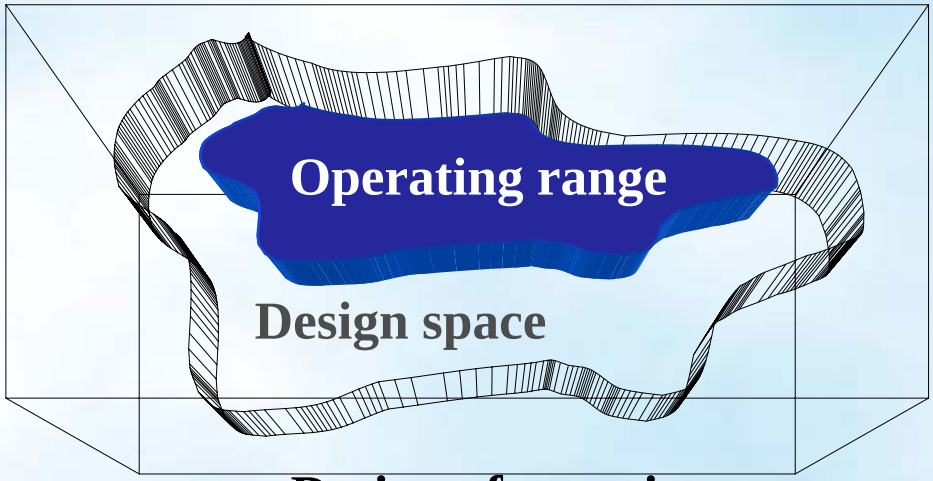
a structured, organized method for determining the relationship between factors affecting a process and the output of that process




# Pharmaceutical development tools

**Design space :**

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




**Design of experiment**

# Pharmaceutical development tools

- Design space:
  - Linkage between process inputs (inputs variables and process parameters) and critical quality attributes
  - Proposed by Applicant
  - Subject to regulatory assessment and approval
  - Implementation before or after MA
  - Established for
    - one or more unit operation(s)
    - up to complete process
  - Working within the design space: not considered as a change

# Regulatory flexibility

- Main regulatory flexibility expected:
  - Revision of "traditional 3 validation batches"
  - Parametric release / skip testing / RTR
  - Implementation of variations without regulatory oversight.

# Regulatory flexibility

- Traditional validation approach on 3 lots:
  - EMEA PAT Q&A:
    - The application of QbD concepts is anticipated to enhance process understanding and monitoring, and thus a state of continuous validation could be achieved.
    - Such approach may therefore be envisaged if adequately justified.

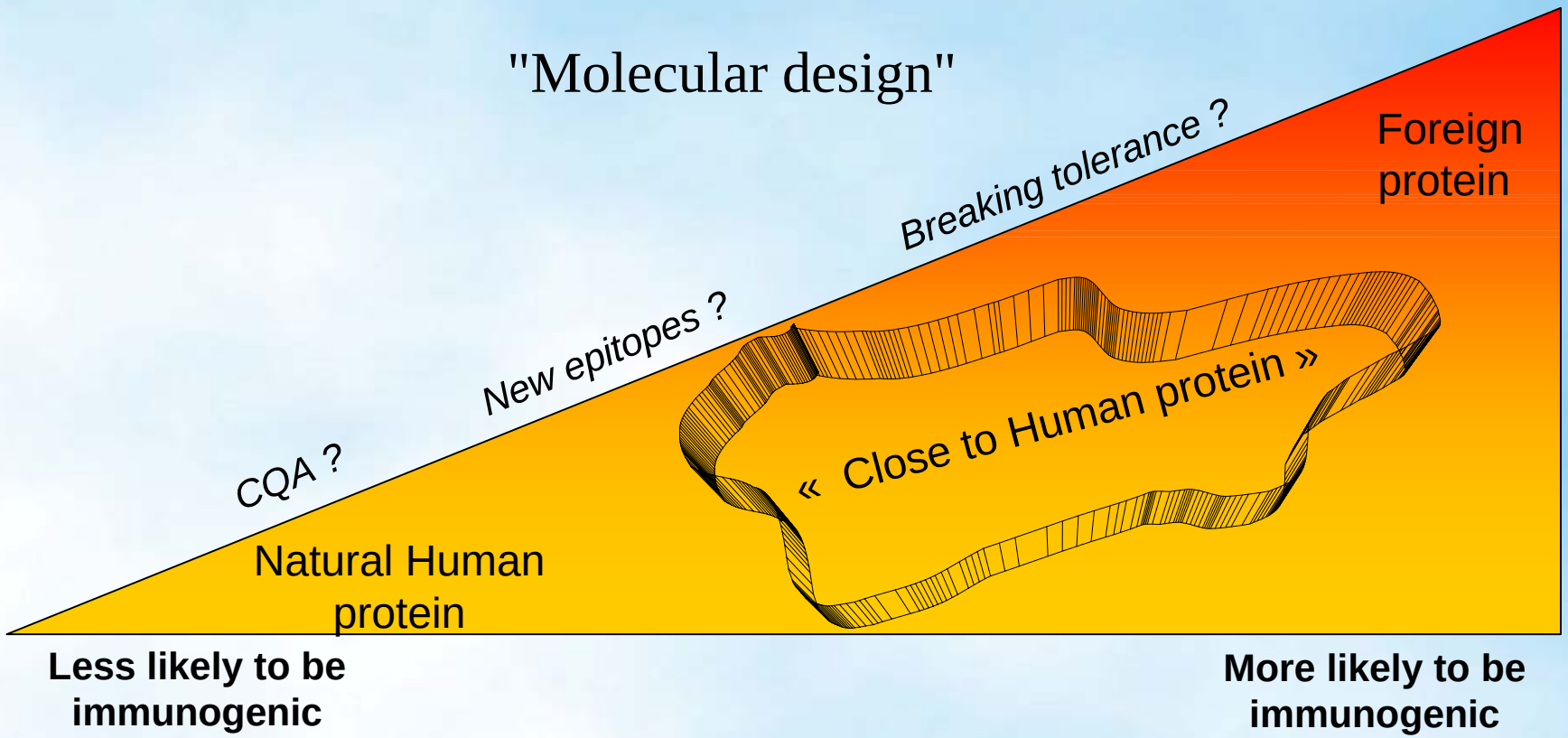
# Regulatory flexibility

- Parametric release / Skip testing / Real time release
  - Application of QbD concepts at release is anticipated
  - Current legislation: must have specifications
  - ICH Q6B:
    - Specifications: critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.
    - Take into account manufacturing process, analytical procedures, product stability, preclinical and clinical studies…
  - QbD concepts vs Q6B:
    - not in disagreement, but
    - When tested, a given product or material must comply with its approved specification

# Regulatory flexibility

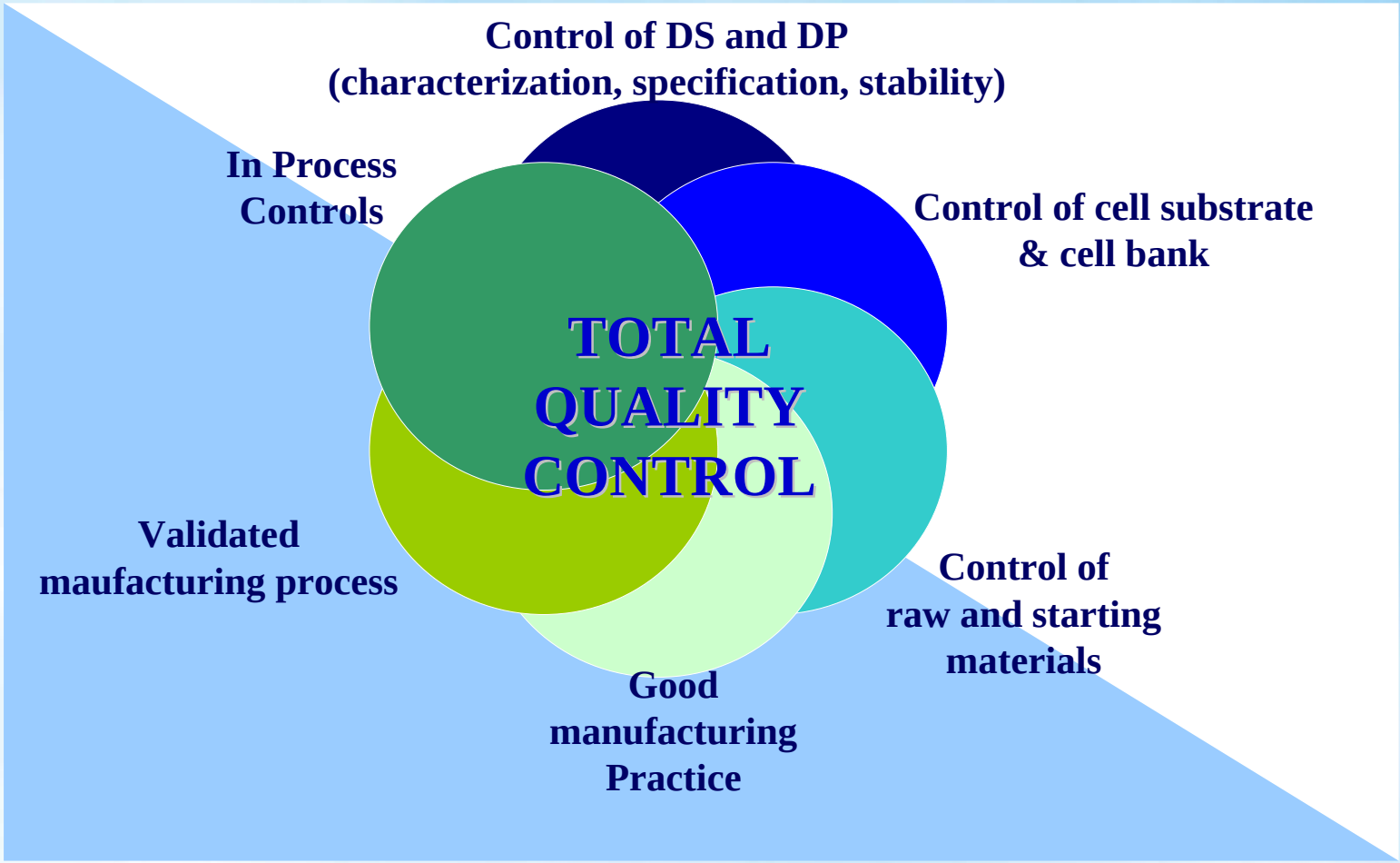
- Implementation of variations without regulatory oversight
  - Design space is proposed by the applicant and is subject to regulatory assessment and approval
  - Working within the design space is not considered as a change
  - Revision of variation regulation: ongoing…

# Biologic's pitfall…



# Biologic's pitfall…

## Biologic's control strategy



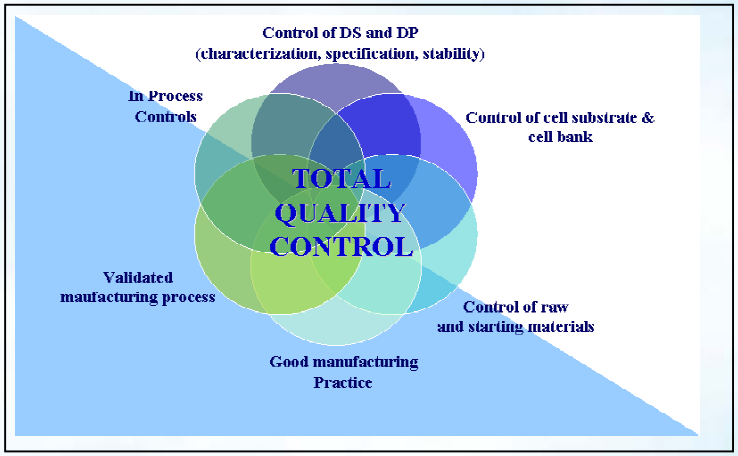

**→ ensure product quality and consistency**

# Biologic's pitfall…

**Comparable ???**

**Suitable ???**

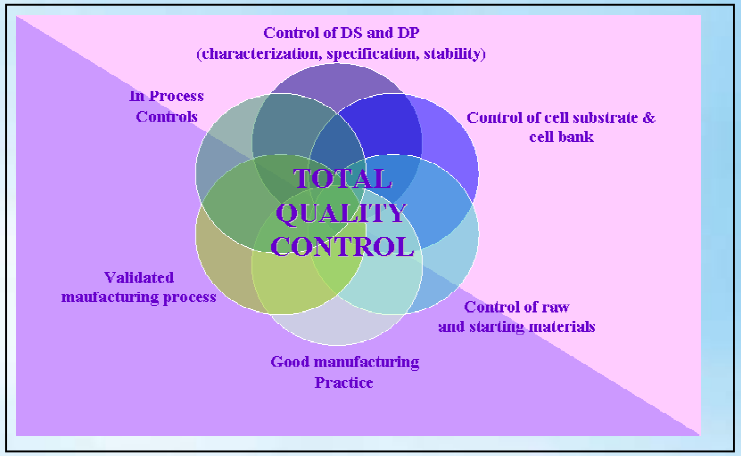
## Product A / Process A




**Safety & Efficacy profiles A**

?

## Product B / Process B




**Safety & Efficacy profiles B**

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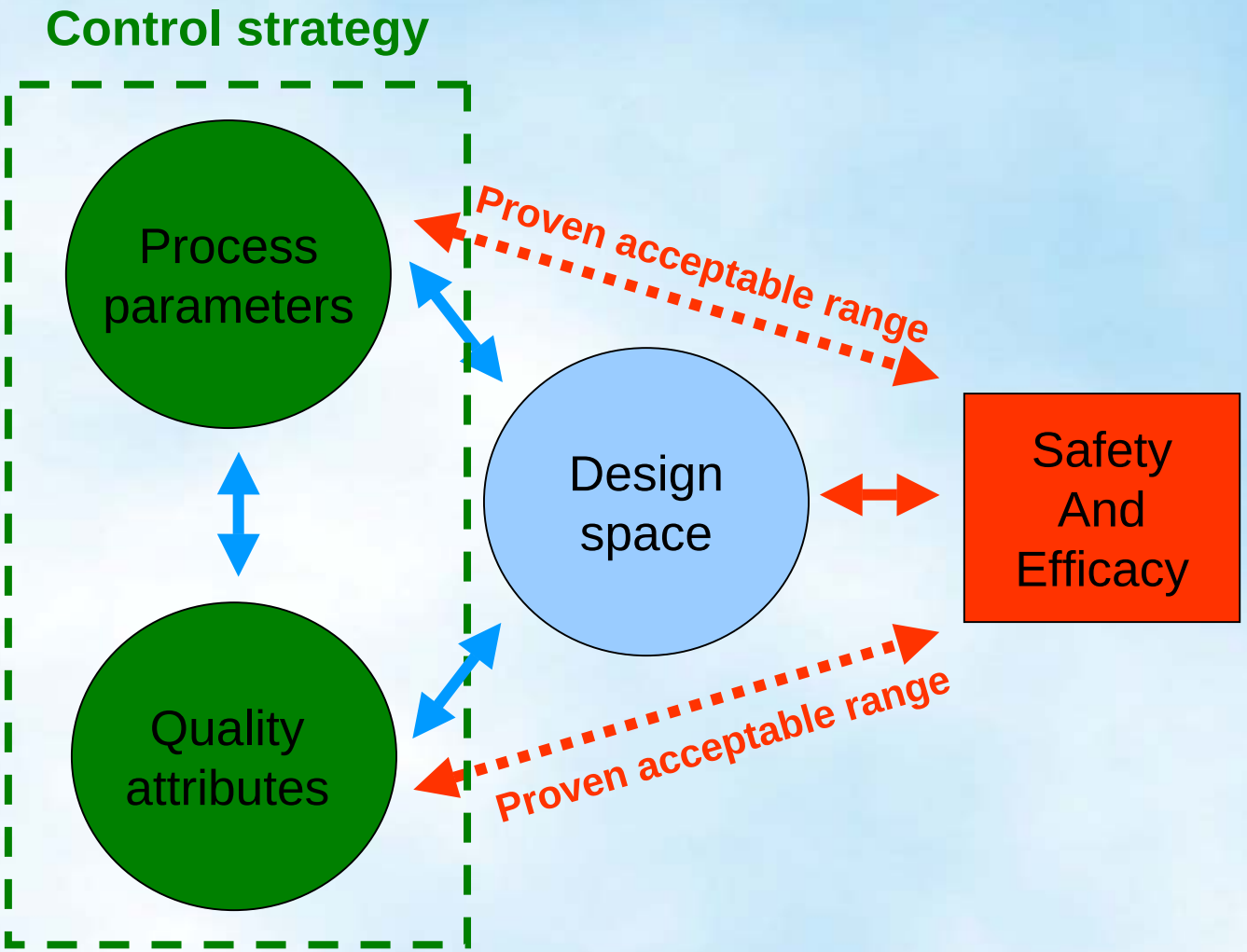
# Biologic's pitfall…



# Workshop on PAT for Biologicals 15th March 2007 - EFPIA Opinion

- Step-wise incremental implementation:
  1. QbD principles systematically embedded within development programs
  2. Design space defined & extended by registration of Acceptable Ranges & Operating Ranges
  3. Pre-submission of protocols to reduce number of unnecessary prior-approval submissions
  4. Establish more relevant and meaningful release specifications
     - Parametric release
     - Skip-lot testing
- Will take some time until full implementation and inclusion in a submission

# Workshop on PAT for Biologicals 15th March 2007 - EFPIA Opinion

- Suitability of the manufacturing process is assured by incremental process knowledge obtained throughout development and confirmed through commercial manufacture
- Immediate opportunity:
  - Submission of protocol as part of MAA as for NCEs
  - Validation of process on first 3 commercial lots (peri- or post-approval)
- Medium term opportunity:
  - Shift focus toward continuous quality & process verification instead of one-time reliance on 3 conformance lots
  - Use of statistical tools (cf. ICH Q9) to further process understanding