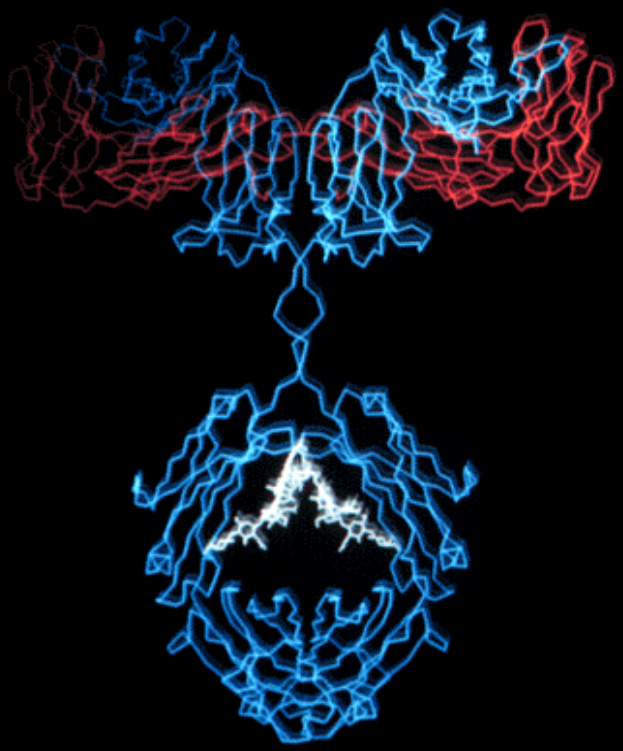
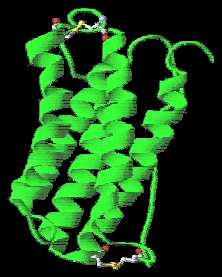
Key considerations for a biological product

K. Ho, CHMP Biologics Working Party

Quality control of biologics



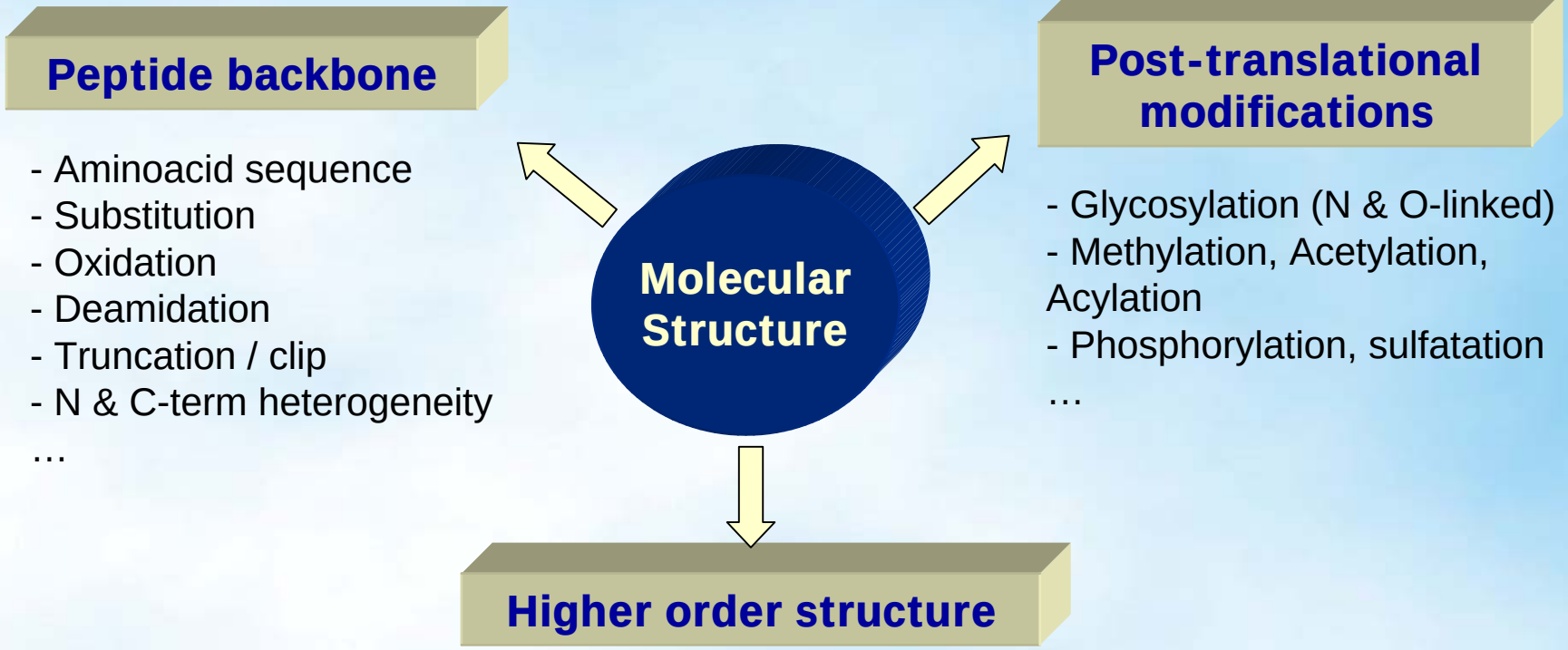
IgG
~660AA, MW: ~150 000 Da



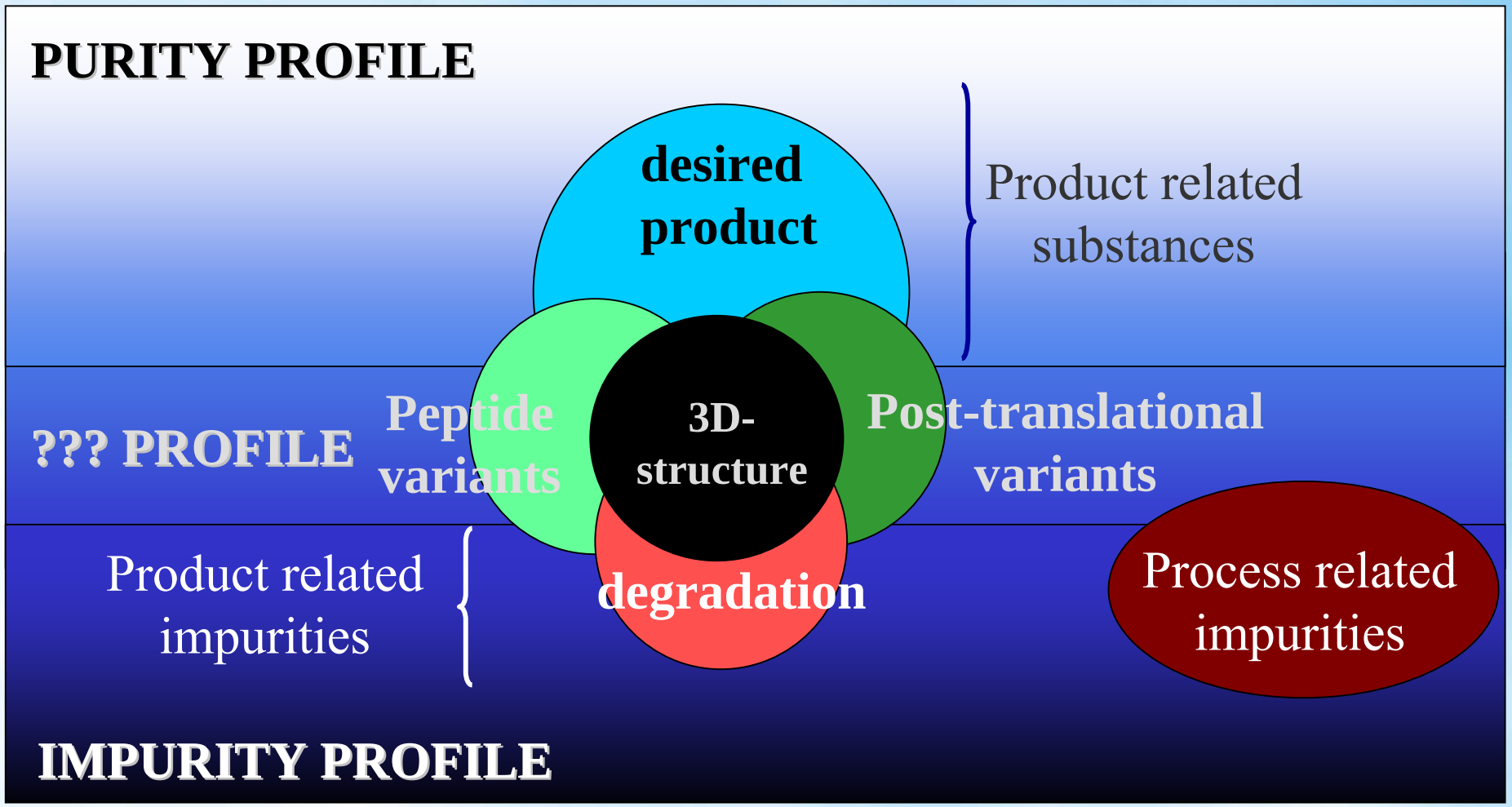
Interferon alfa,
165AA, MW: 19 625 Da

Aspirin,
MW: 180 Da

Quality control of biologics



Quality control of biologics



Quality control of biologics

Quality control of biologics

To acquire knowledge of the
desired product, product variants and impurities …

⇩

Appropriate design of experiments

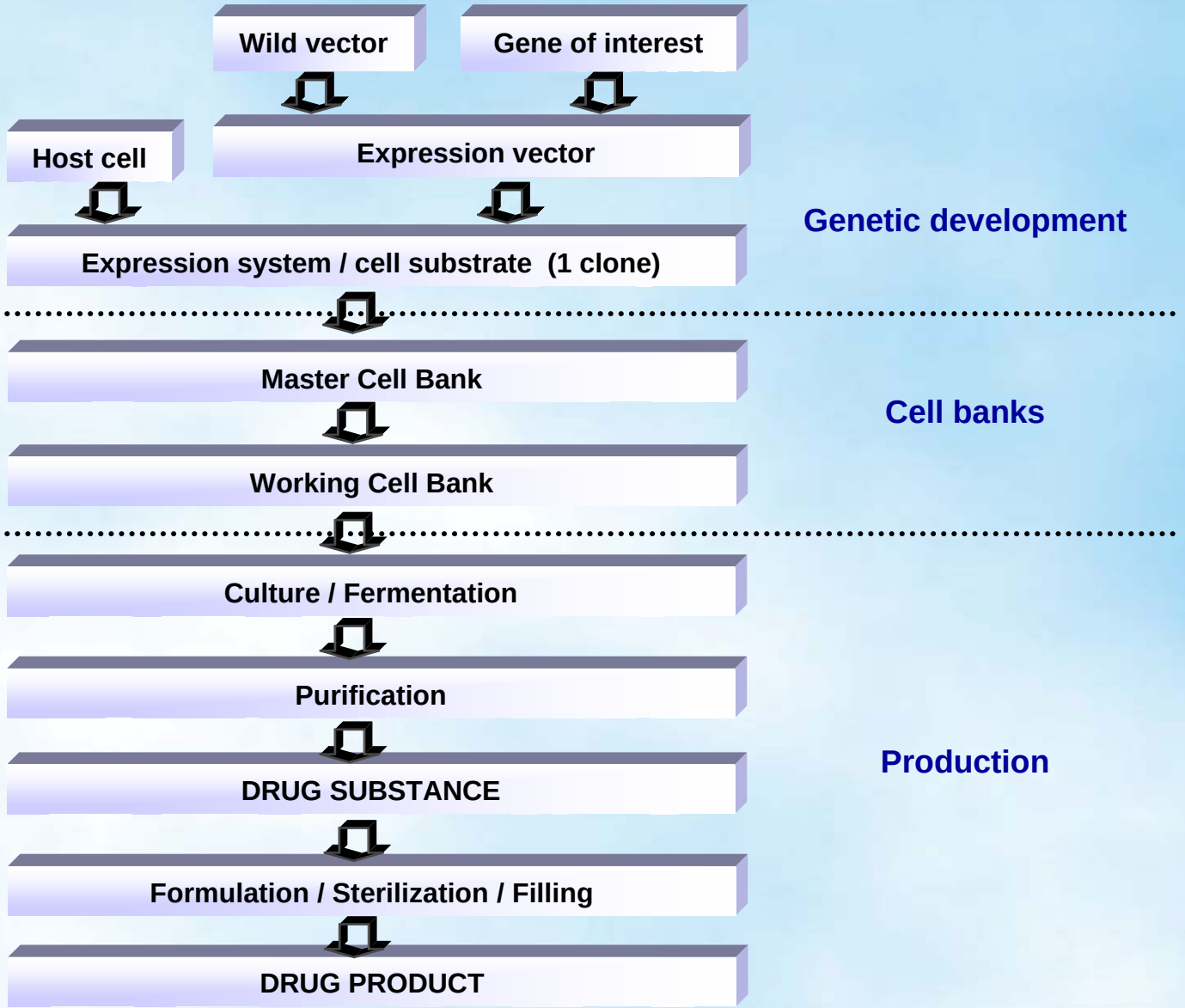
+

Appropriate analytical tools

+

Understanding of manufacturing process…

Manufacturing process



Genetic development
(ICHQ5D)

- ***Origin, source and history of the cell substrate***
  - **Cell substrate**: *"microbial cells or cell lines derived from human or animal sources that possess the full potential for generation of the desired biotechnological/biological products for human in vivo or ex vivo use"*
  - **Research & development information**: published data, historical data from source laboratory, and experimental data
  - **Characteristics of the cell substrate**: species, strain, genotypic and phenotypic characteristics, generation level, pathogenicity, toxin production, biohazard…
  - **Biological purity**: exposure to infectious agents (contact with biological constituent?)
- ***Generation of the cell substrate***
  - Procedure(s) used to obtained the cell substrate (transfection, selection…)

Cell banking
(ICHQ5D)

- ***Cell Banking system***
  - Two-tiered system: most common approach
  - MCB: directly derived from an initial clone
  - WCB: prepared from 1 or more vial of MCB
- ***Cell banking procedures***
- ***Characterisation and testing***
  - Identity
    - Phenotypic and/or genotypic characteristics
    - All possible tests: not necessary
    - Performed on MCB and/or WCB
  - Purity
    - Free from adventitious contaminants

Genetic stability
(ICHQ5B)

- ***Stability and consistency at/or beyond production level***
  - ***Cell substrate***
    - Stable from cell bank to the end of fermentation and/or beyond
    - No change in the expression construct (DNA sequence, restriction map…)
  - ***In process control***
    - Consistency of production runs (growth, productivity, plasmid copy number, glucose consumption…)
  - ***Protein analysis***
    - Consistency
    - Product related analysis (AA substitutions, isoforms …)
    - Analysis of translational & post-translational events
- ***Limit of cell age to be defined***

Production

(Production and Quality Control of Medicinal Products derived by recombinant DNA Technology, 3AB1a)

- ***Batch definition***
- ***Detailed description***
  - Process + In-process controls (process parameters + quality attributes)
  - Control of microbial contamination at suitable stage
  - Suitability of methods
  - Raw materials / material of biological origin
  - Reprocessing
  - Hold times
- ***Validation***
  - Consistency
  - Capacity to remove unwanted impurities (e.g. host cell protein, nucleic acids, carbohydrate…)
  - Working conditions (column load, cleaning, regeneration…)
  - Sterilization, aseptic filling, lyophilisation…
- ***Adventitious agents safety evaluation*** *(ICH Q5A)*
  - Control of endogenous and adventitious agents
  - Validation of elimination and inactivation

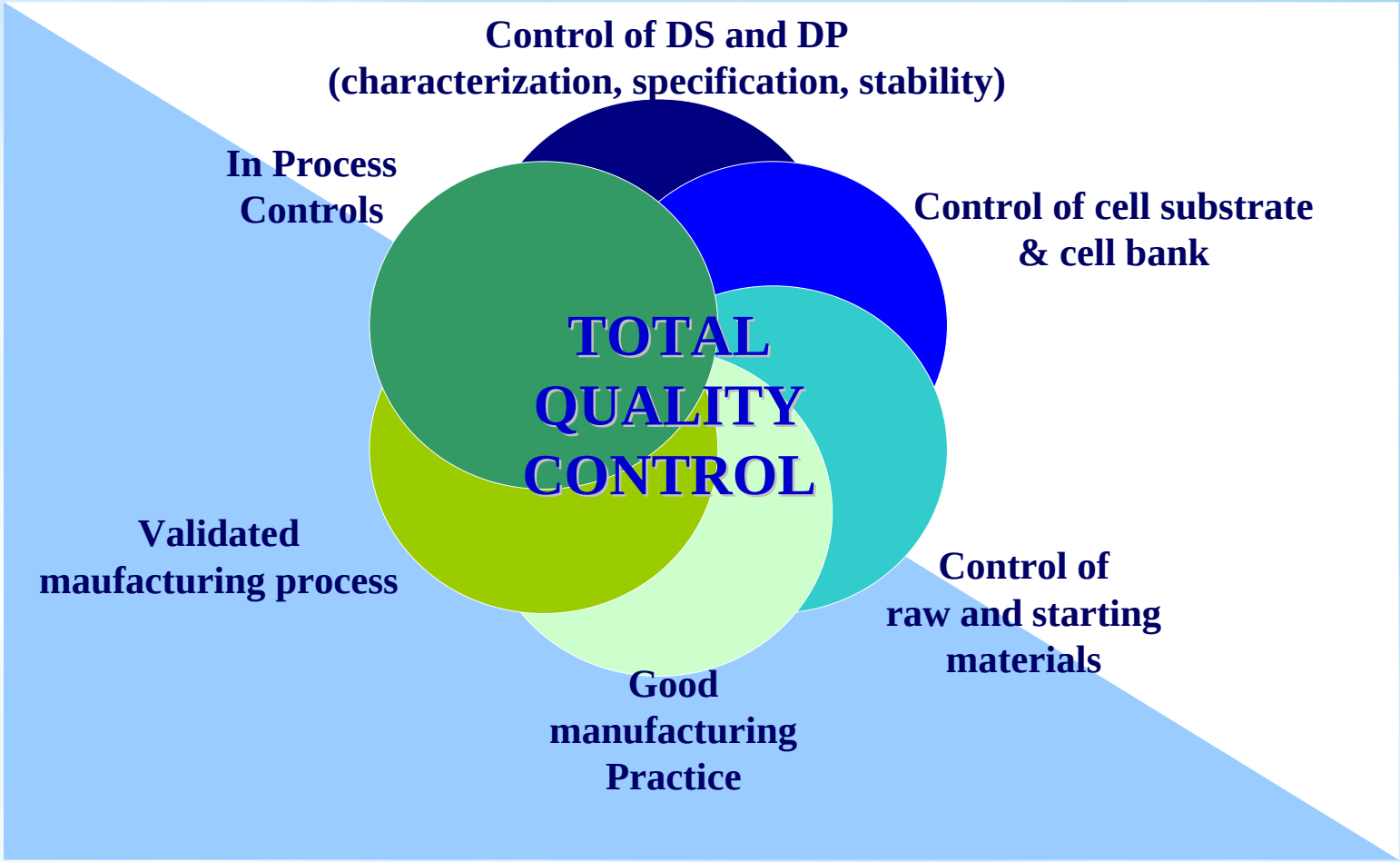
"Biotech paradigm"

- Analytical challenge:
  - Complex purity/impurity profile
  - Depend on manufacturing process and product
  - Many unknowns

- Manufacturing challenge:
  - One change… a cascade of changes…
  - Necessity to reconsider downstream steps
    … and upstream steps, as appropriate

- Biotechnology derived products are defined by
  the product and… its process

Biologic's control strategy
(ICH Q6B)

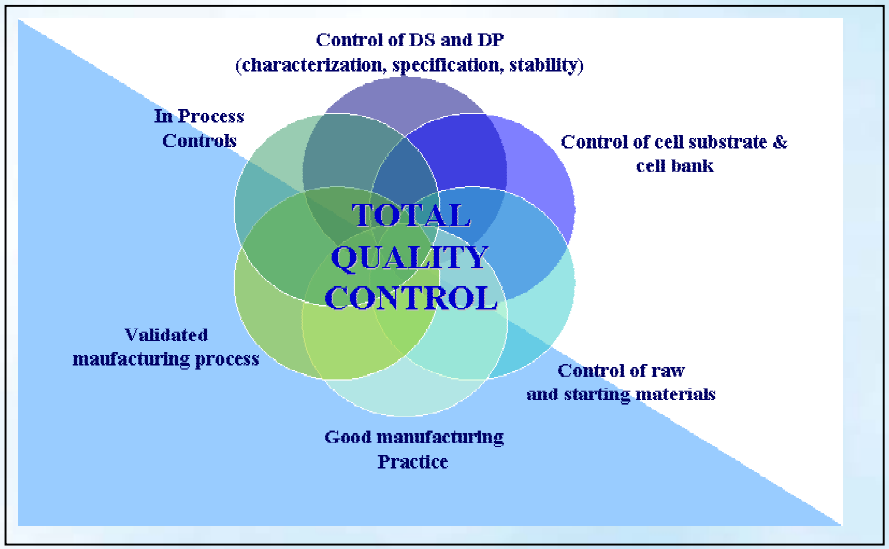


→ ensure product quality and consistency

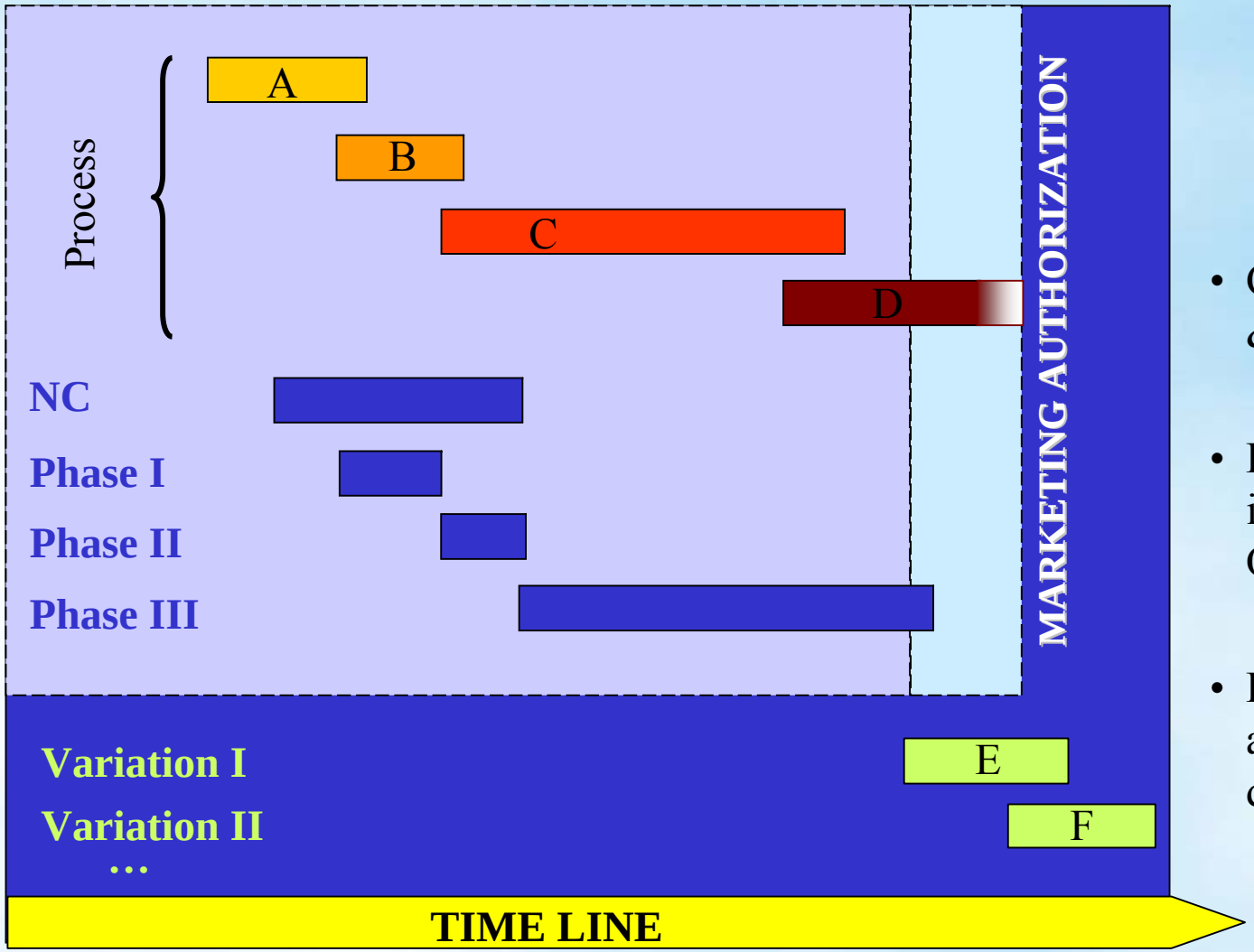
Quality assessment

Safety & Efficacy profiles

Clinical experience



Process development



Life cycle of a product:

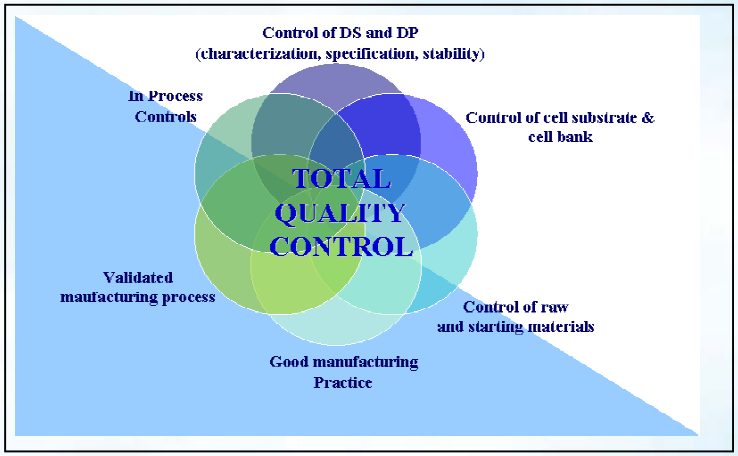
- Continuous research & development
- Frequent improvement of Quantity / Quality
- Parallel Non-clinical and clinical development

Process development

Comparable ???

Suitable ???

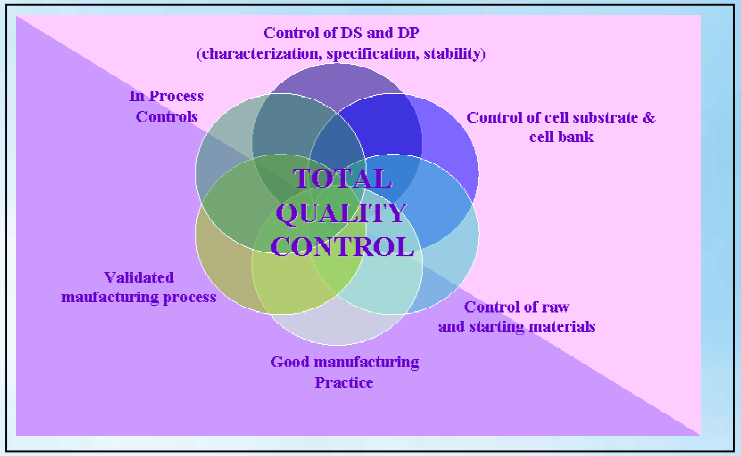
Product A / Process A



Safety & Efficacy profiles A

?

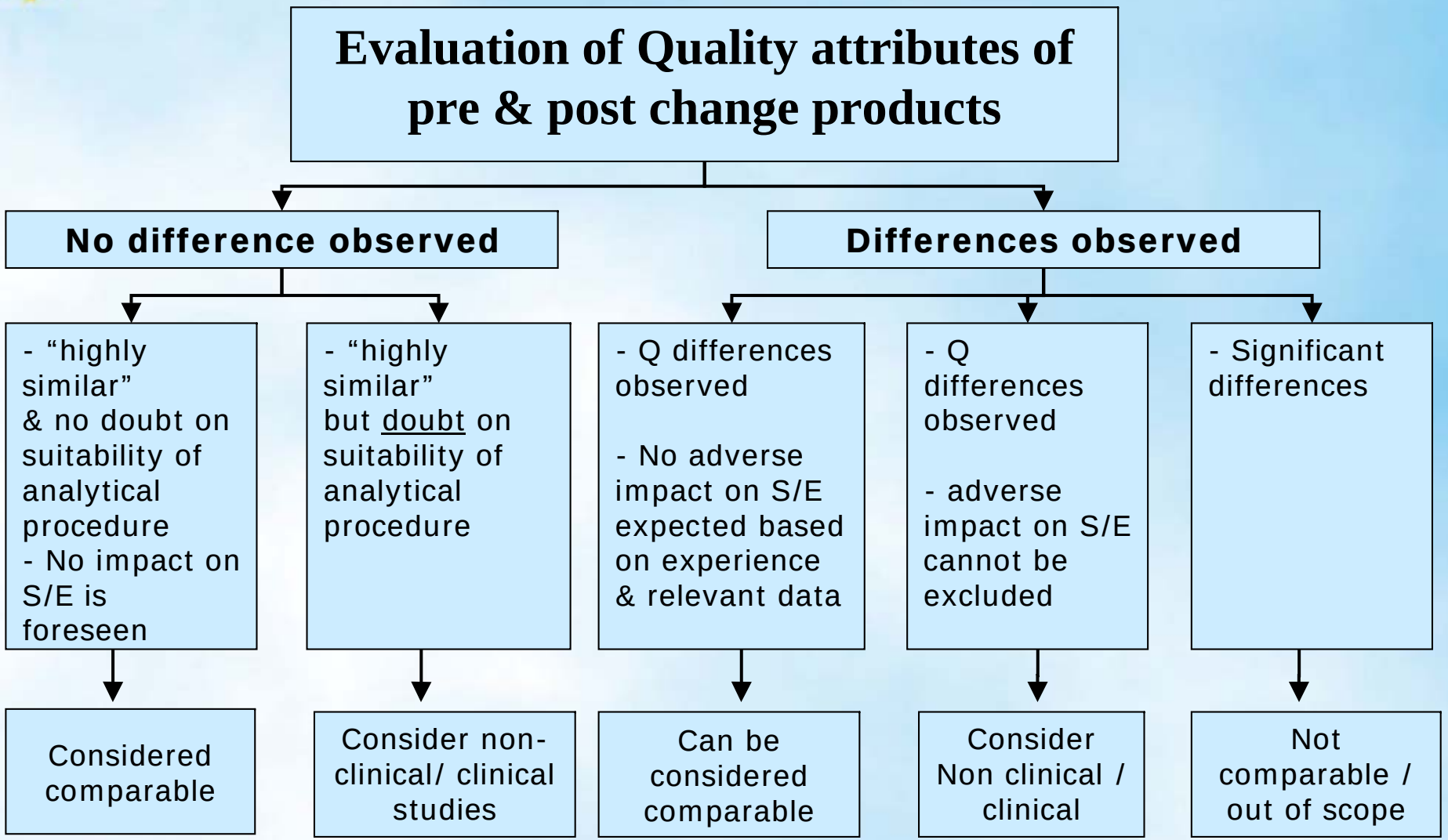
Product B / Process B



Safety & Efficacy profiles B

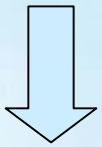
?

Comparability exercise (ICH Q5E)



Comparability exercise (ICH Q5E)

Data expected*



Comparability exercise

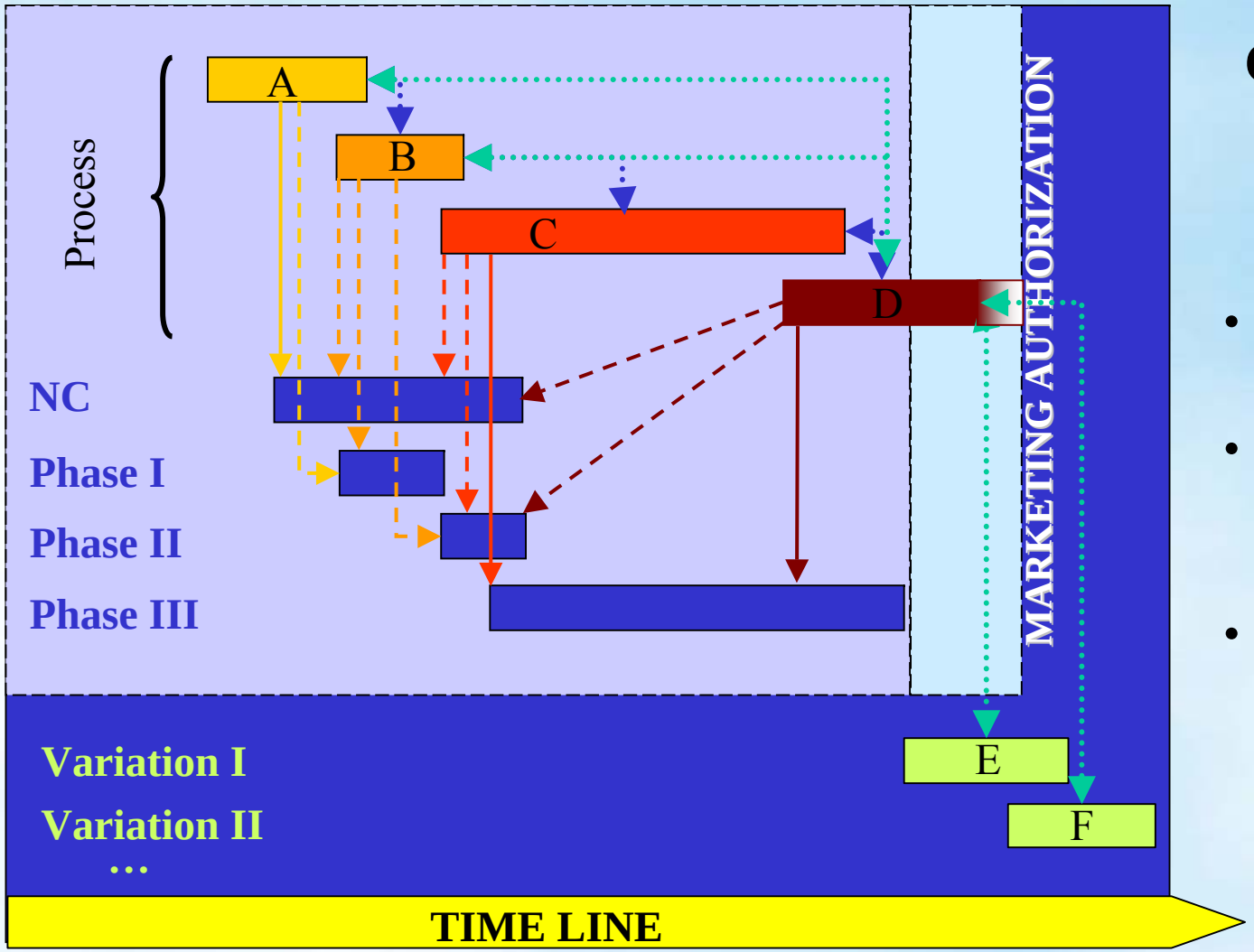
(Q ± S ± E)

+

Process considerations

* *Depends on stage of development*

Process development



Comparability exercise during development

- Tool for risk assessment +++
- "Comparable" ≠ "Suitable" for a given stage
- Requirements increase with development stage…

Requirements

MARKETING AUTHORISATION

Phase III

Phase II

Phase I