Innovator or Biosimilar – Assuring Comparability During Development of Biologics

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What makes biologics different?

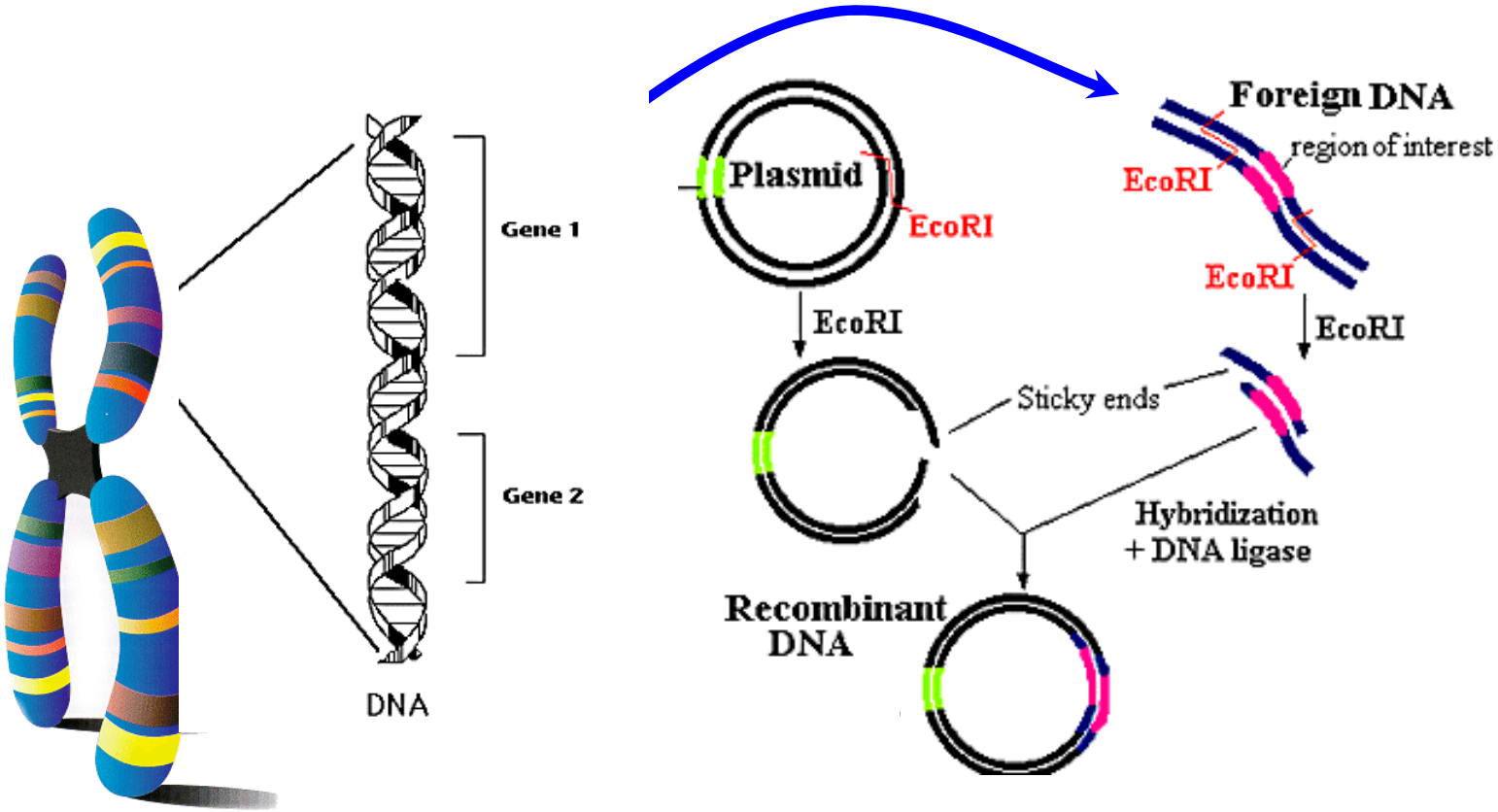
- Biologic medicines are derived from living systems
- Immunogenicity – the ability to provoke an immune response
- Very complex manufacturing processes – changes in manufacturing process can result in *very* different end product

Manufacturing 101

The Making of a Biopharmaceutical

A Factory within a Factory

- Making the blueprint

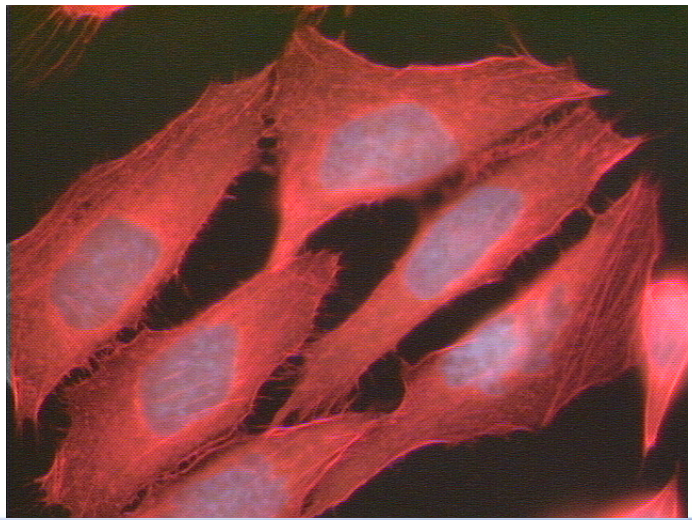


A Factory within a Factory

- Selecting the mini factory - the host cell
  - Laboratory strains engineered to exhibit qualities favourable to bio-manufacturing

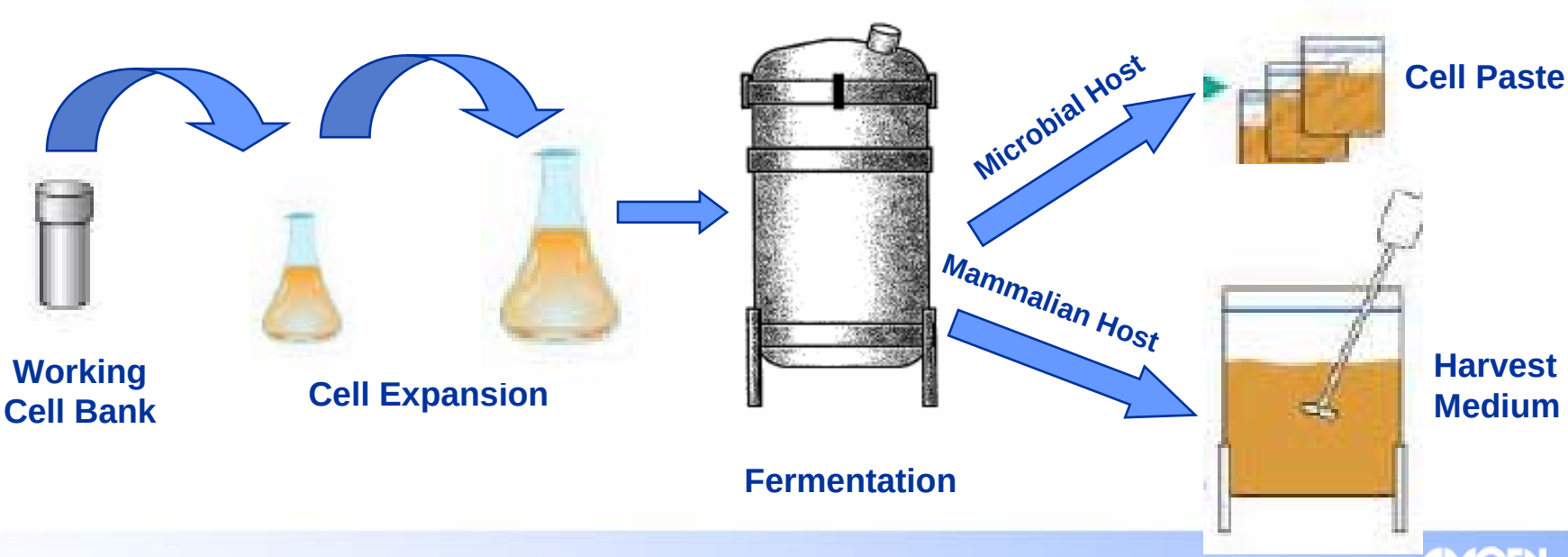
Microbial host: *E. coli*

Mammalian host: Chinese Hamster Ovary (CHO) cells



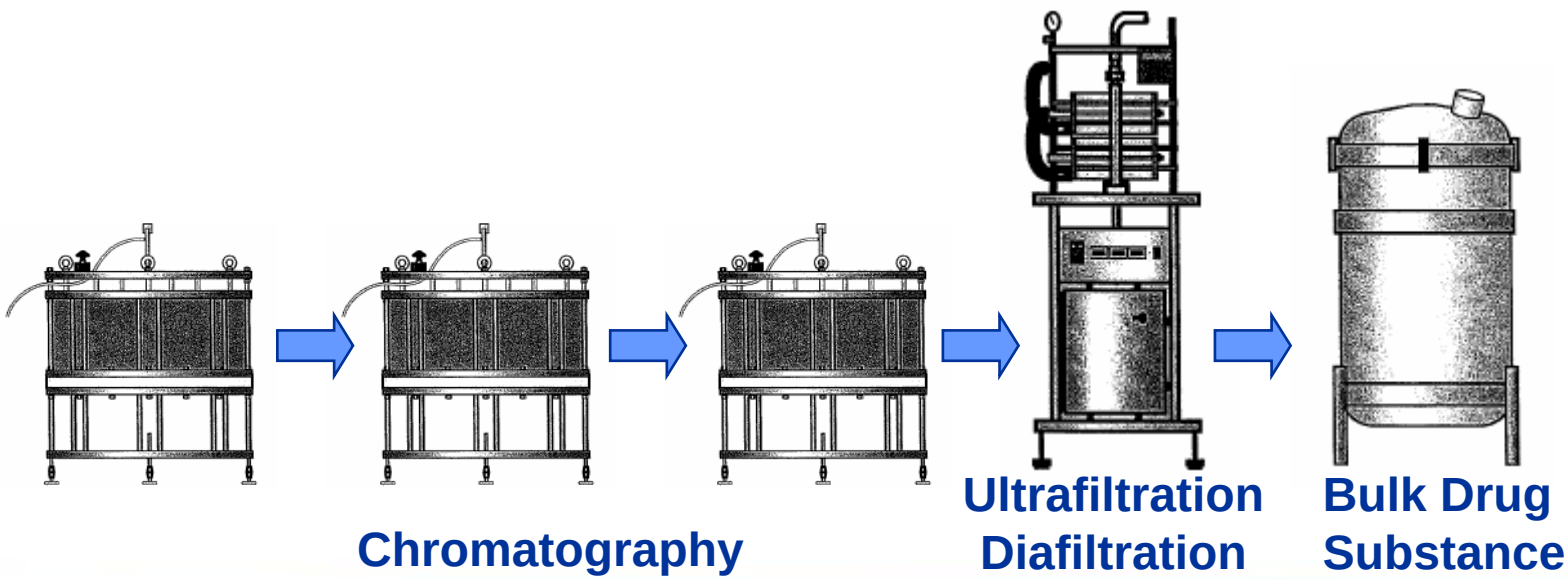
Milestones of Biological Manufacturing Process -- Cell Culture

- Cell culture expansion – increase the number of protein-generating units
- Protein production – induce the cells to manufacture protein
- Harvest – collect the protein
  - Microbial cultures: Collect the cells / throw away broth
  - Mammalian cultures: Collect the broth / throw away the cells



Milestones of Biological Manufacturing Process -- Purification

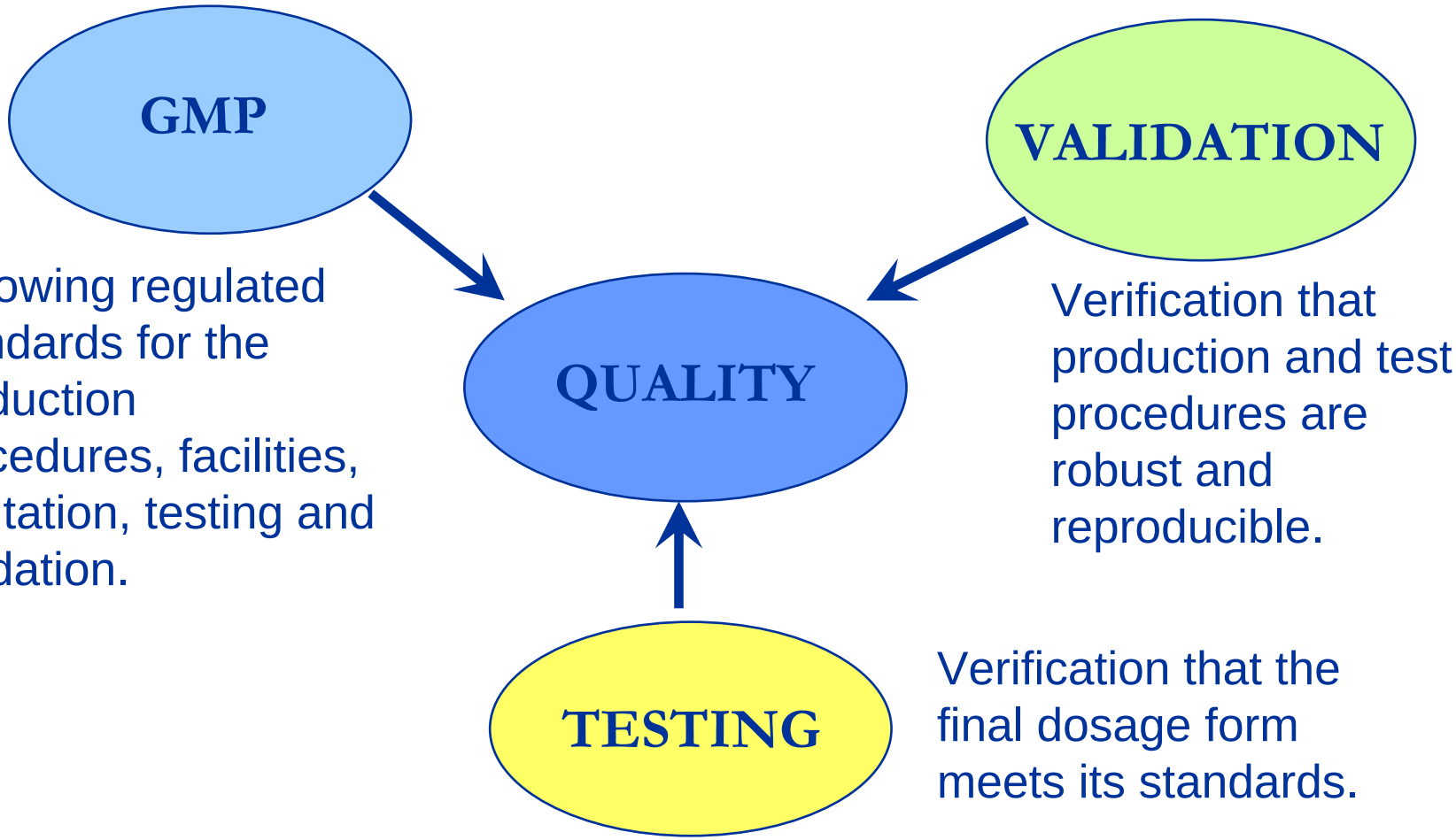
- Remove Process-Related Impurities
  - Growth media
  - Cell debris
  - Soluble host cell contaminants
  - Other reagents
- Remove Product-Related Impurities
  - Variant forms of the protein, e.g. dimers, clipped forms, biochemical variants



Milestones of Biological Manufacturing Process -- Formulation, Fill and Finish

- Formulation into Dosage Form
  - Concentrated protein is diluted with formulation buffer, or
  - Buffer is exchanged via diafiltration
- Fill and finish
  - *Aseptic process* – sterilization by filtration, into sterile primary container
  - Solution in vials or syringes, or freeze-dried (lyophilization)

Ensuring Quality

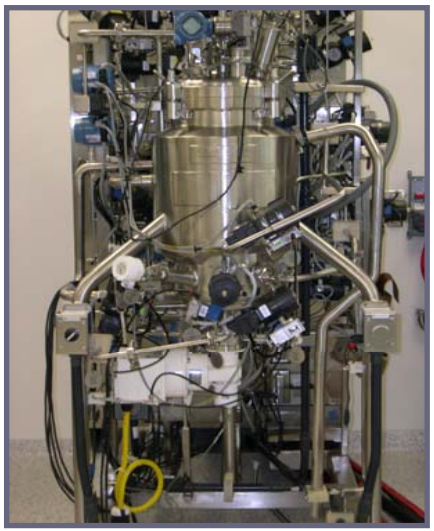


Following regulated standards for the production procedures, facilities, sanitation, testing and validation.

Verification that production and test procedures are robust and reproducible.

Verification that the final dosage form meets its standards.

Defining Comparability



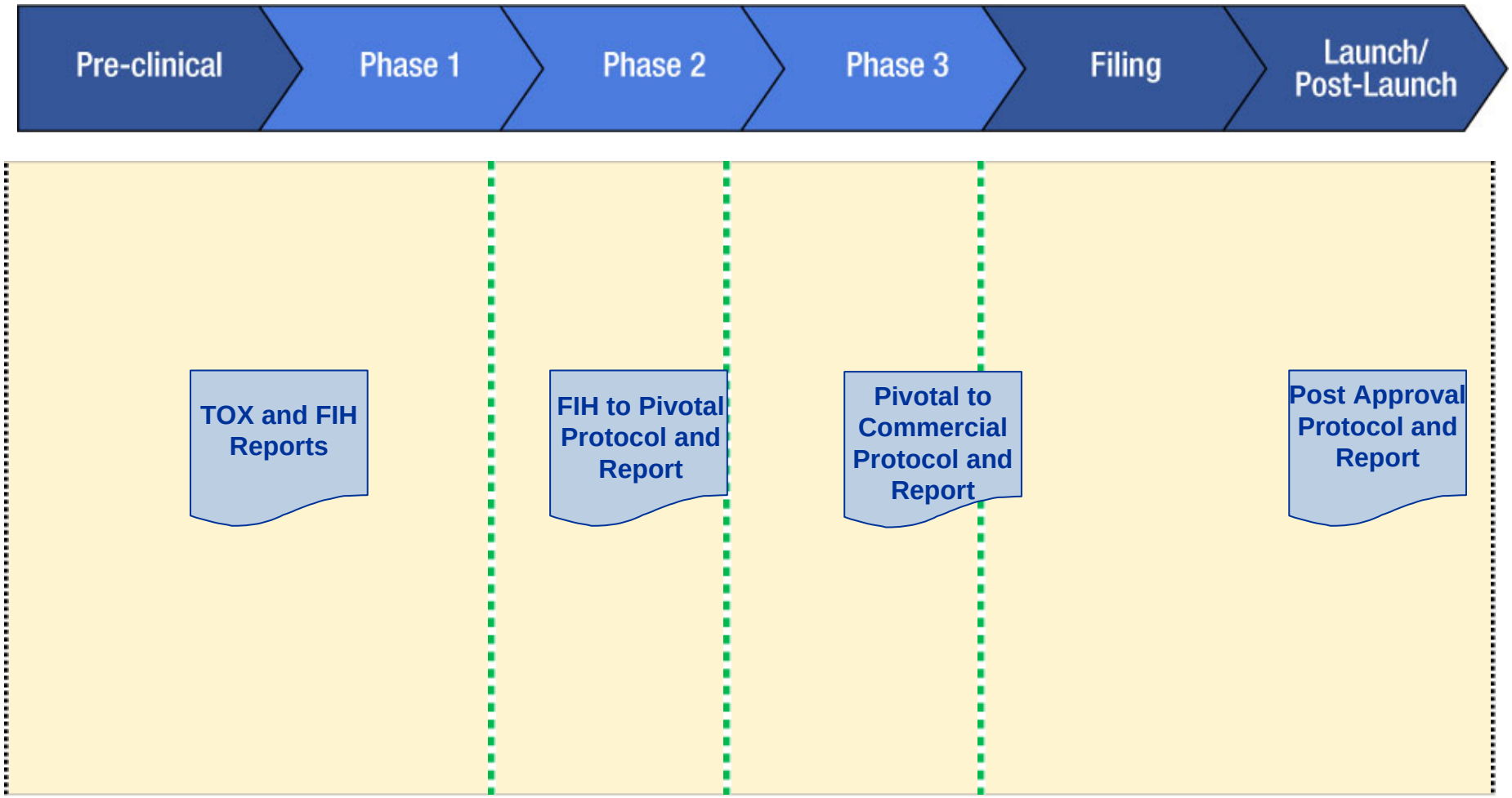
What is Comparability?

- The process of demonstrating that products have highly similar quality attributes e.g., ***before and after process changes***

Comparability needs to take several "histories" into account…

- **Product development history**, from toxicology studies, clinical, commercial and post approval
- **Process development history**, and comparisons of process performance capabilities
- **Method development history**, and the impact on product and process characterization

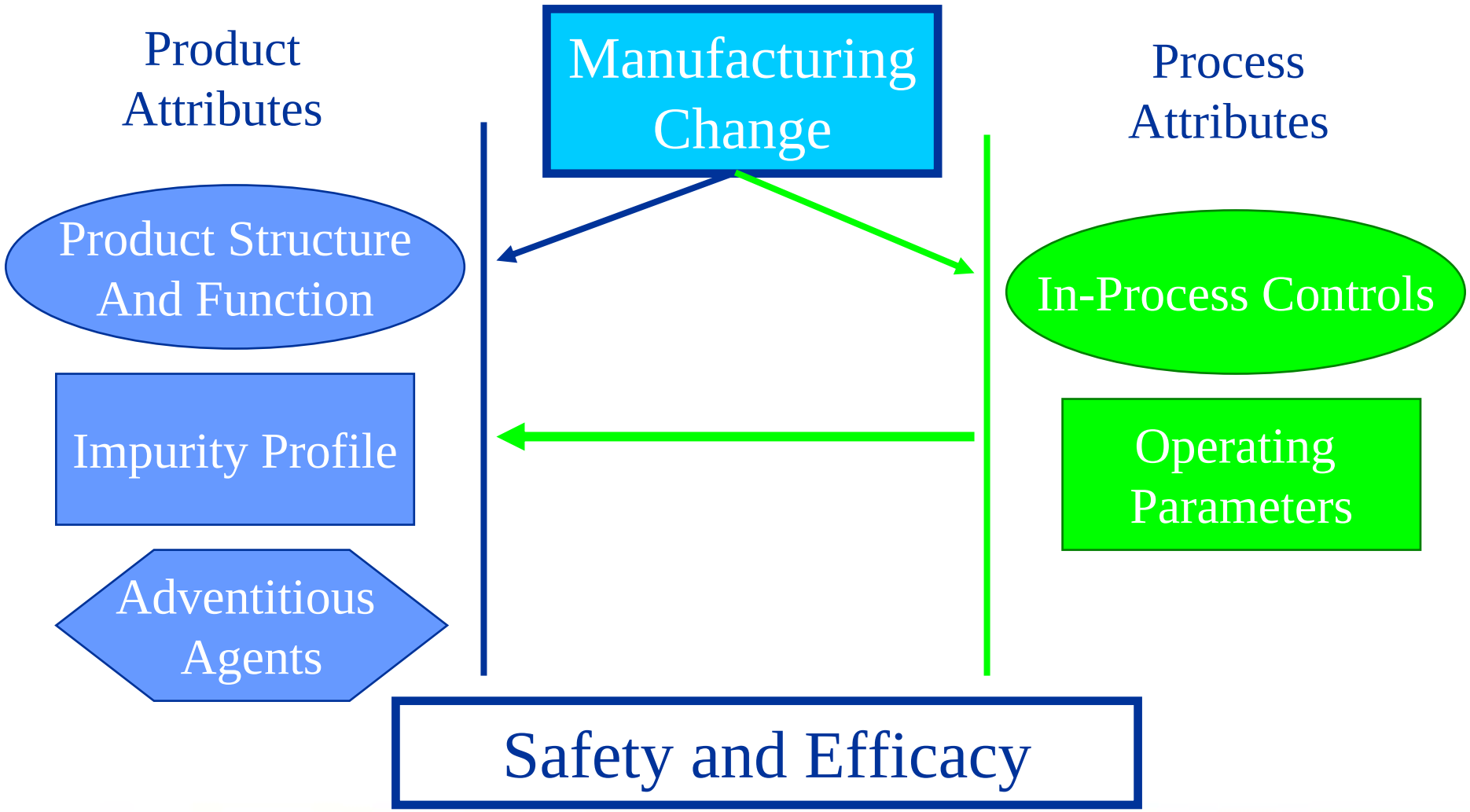
Comparability Assessment is a Process Throughout Development



Comparability After a Process Change - Three Questions

1. Will the proposed process change alter the capability of the process to produce the same product?
2. Has the process change altered the product?
3. How does a change in product affect safety and efficacy?

Assessing Results of Changes to Manufacturing Processes to the Product and Process



Development of Comparability Studies

- Understanding the need for change *e.g.* yield, purity, site change
- Must:
  - Define critical and non-critical process parameters
  - Consider how the process impacts those parameters
  - Monitor parameters appropriately
  - Ongoing monitoring

to result in more controlled manufacturing changes and **predictable product outcomes**

Development of Comparability Studies

- The most important element of the comparability study is the **planning** that goes ahead of the study
- One needs to develop a comparability plan / protocol that states **up front** what the intention of the study is and includes all elements of the study, including **acceptance criteria and their justification**
- A risk assessment is a valuable tool to understand the potential impact of any change

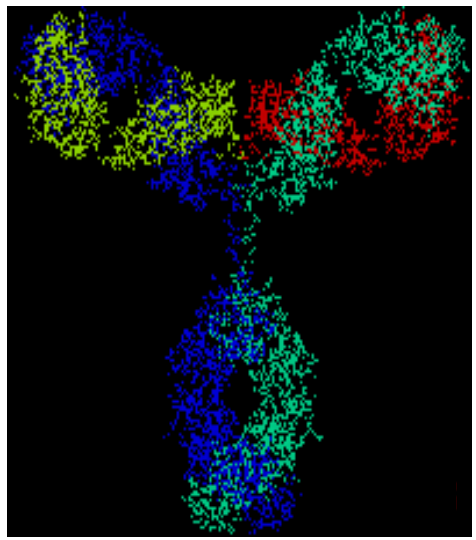
Comparability Protocols – Process

- **Process comparability**
  - What data on **process performance** do you have to support the change (very important)?
  - What data should you compare -- what is critical?
    - IPC's
    - operating parameters
  - How to compare?
    - how many data points?
    - acceptance criteria and justification
    - statistical plan

Same complexity for innovator and biosimilar

Comparability Protocols – Product

- **Product comparability**
  - What data do you have on **product parameters** to support the change (very important) – your 'Key Quality Attributes'
  - What data should you compare
    - lot release tests
    - characterization tests
  - How to compare?
    - how many data points?
    - acceptance criteria and justification
    - statistical plan

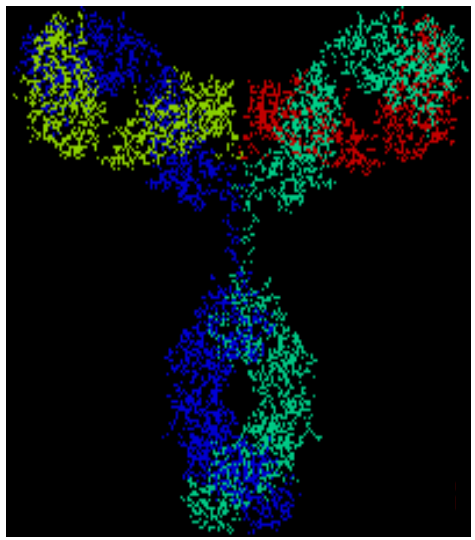


Comparability Protocols – Product: Biosimilar Specific Issues

- **Product comparability**

Biosimilars will need dual comparability programs - **within** their own product development, and **against** innovator product…

but will not know the key quality attributes of the innovator's product

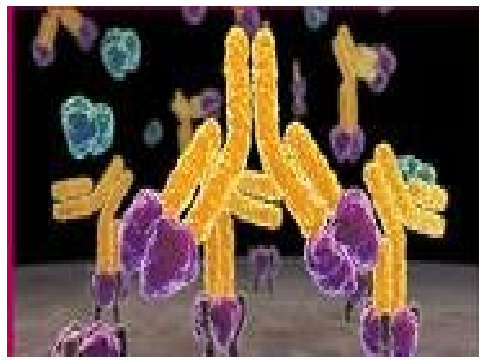


Comparability Protocols - Immunogenicity

- **Immunogenicity**

  Comparability and assessment of immunogenicity during development relies heavily on:

  – analytical characterization,
  – design of preclinical and clinical studies
  – design of the assays used to detect and characterize antibodies
    - Format (RIA, ELISA)
    - Sensitivity
    - Positive control
    - Positivity criteria
    - Timing and number of samples

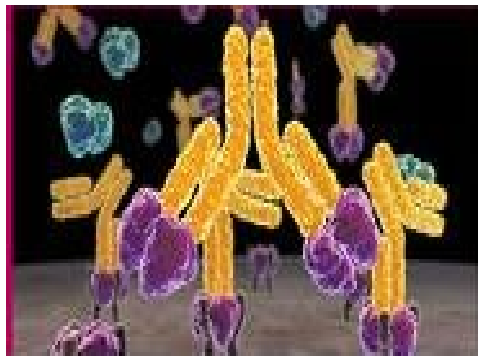


Comparability Protocols – Immunogenicity: Biosimilar Specific Issues

- **Immunogenicity**
  - A biosimilar will have the same challenges as the innovator to show comparable immunogenicity during development, but *much more difficulty comparing against the innovator data*

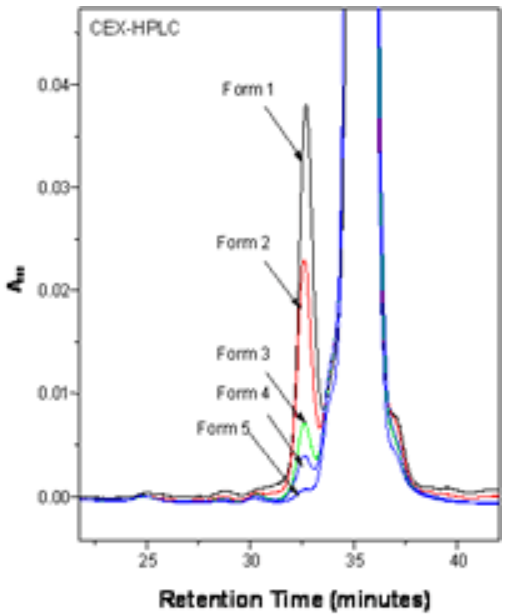
The biosimilar does not have knowledge of the innovator's analytical techniques:

Assay format, sensitivity…
Criteria for positivity
Timing and number of samples



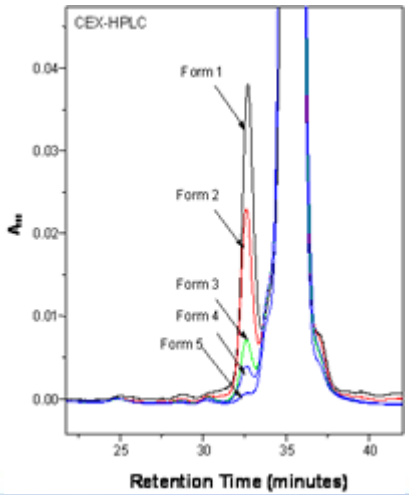
Comparability Protocols – Methods

- **Method comparability**
  - Method development / validation and the suitability to assess comparability
  - What data to compare?
  - Do you have sample retains?
  - Can you use old data?
  - Acceptance criteria and justification – do your methods have the appropriate evaluation to support comparability? (e.g. conforms to standard, visually similar, etc.)
  - Statistical plan



Comparability Protocols – Methods: Biosimilar Specific Issues

- **Method comparability**
  - The biosimilar does not have access to the exact methods used by the innovator
  - How can one assure that the results used in comparability studies between innovator and biosimilar can pick up relevant quality attributes, as methods can differ by capabilities such as:
    - Sensitivity
    - Specificity
    - Resolving power
    - Data analysis



Comparability Protocols – Risk Assessments

- **Risk Assessments**
  - How well do you understand the relationship between **product characteristics** and **safety and efficacy?**
  - Patient Population - disease state
  - Therapeutic window
  - Treatment regimen
  - Impacts of immunogenicity

Conclusions

- Development of a biotechnology drug product poses unique challenges
- These challenges impact both innovator and biosimilar

Up-front definition and design of comparability studies is critical