

The logo for Celerion features a stylized, flowing maroon wave above the word "celerion" in a lowercase, sans-serif font. The wave starts on the left, rises to a peak, and then descends towards the right, ending just above the letter 'i'.

celerion

# **Scientific Challenges for Development of Biosimilar Monoclonal Antibodies**

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# Presentation outline

- Biosimilars – Definitions and Concepts
- Regulatory Framework
- Bioanalytical assay development considerations
  - PK and Immunogenicity assay development
- Summary

# What does Biosimilar or Biosimilarity means?

- The biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and
- There is no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product.
- Neither the EU legislation nor the EMEA CHMP guidelines provides a definition of a biosimilar other than it is a product comparable in quality, safety and efficacy to a reference product.
- The acceptable differences between biosimilar and reference products in these three major attributes are not stated.

# FDA GENERAL REQUIREMENT

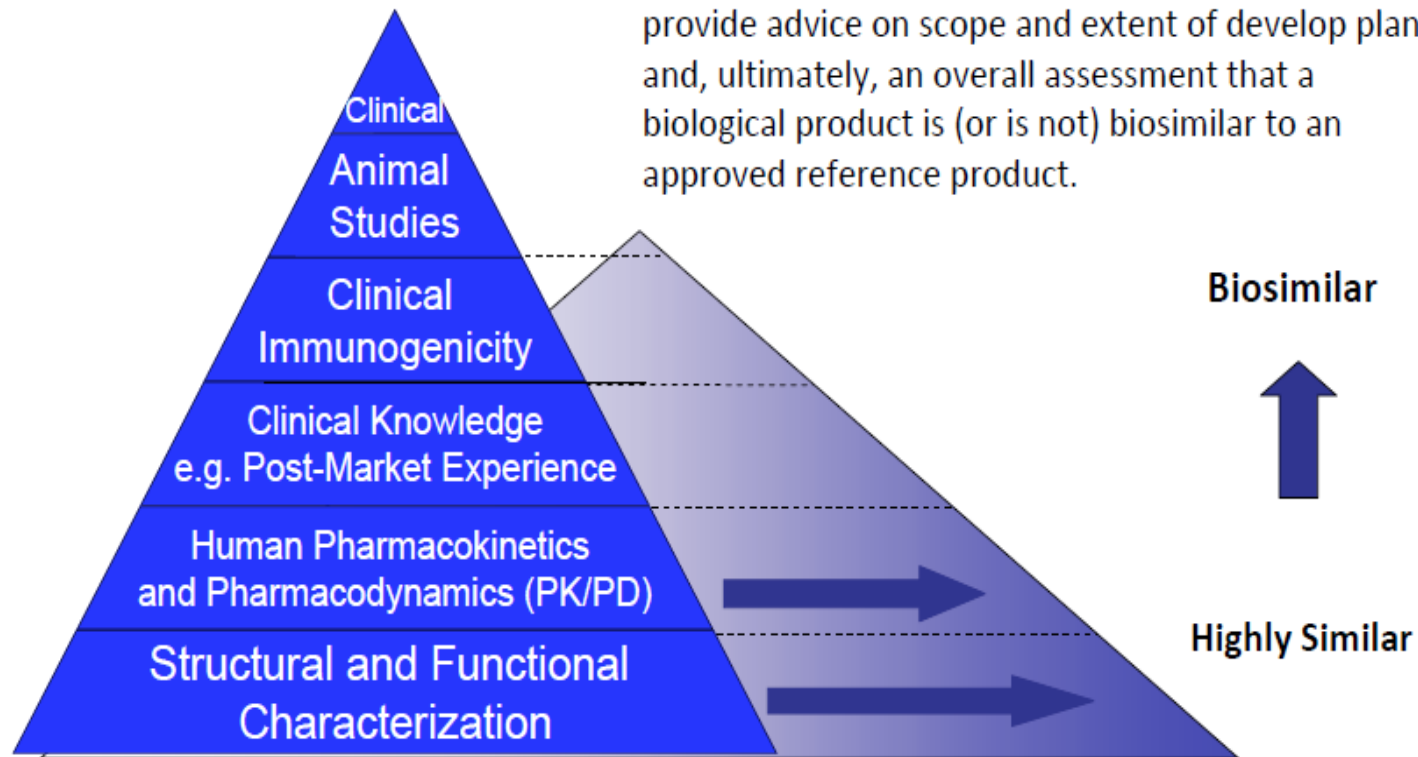
A 351(k) application must include information demonstrating biosimilarity based on data derived from:

- Analytical studies demonstrating that the biological product is “highly similar” to the reference product notwithstanding minor differences in clinically inactive components;
- Animal studies (including the assessment of toxicity); and
- A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed.

*FDA may determine, in its discretion, that an element described above is unnecessary in a 351(k) application.*

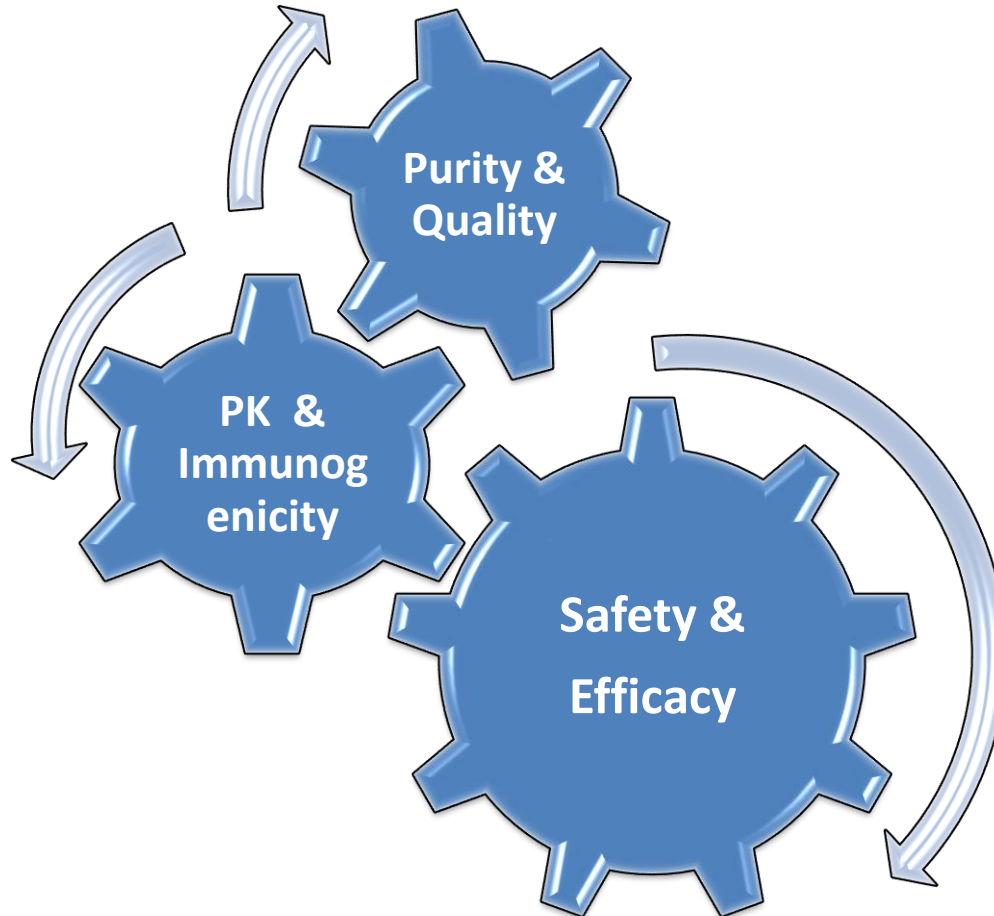
# Totally of the Evidence

## Totally of the Evidence



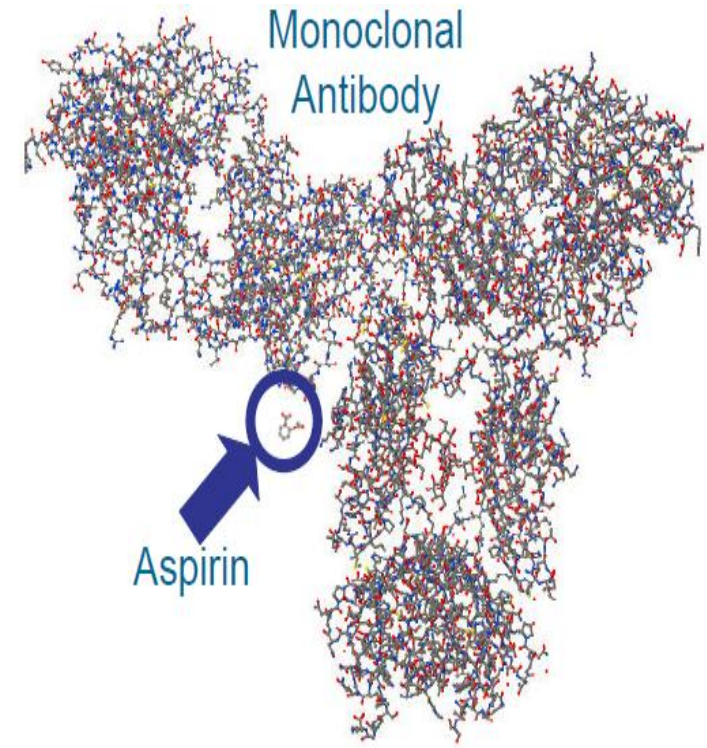
# Importance of Bioanalytical Data

- Accurate and precise bioanalytical data is critical to establishing comparability between biosimilar and innovator products.

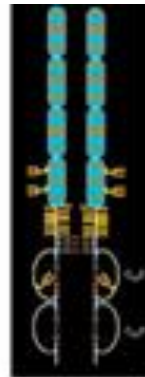


# Monoclonal Antibodies

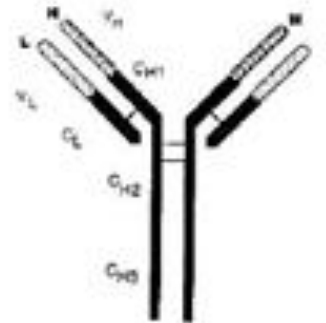
- Monoclonal antibodies have been established as a major product class of biotechnology-derived medicinal products.
- Different mAb products share some properties, e.g. being cytotoxic to their target, or neutralizing a cytokine, but differ in aspects like the mechanism of action.
- They are structurally complex, and may have several functional domains within a single molecule, depending on the Isotype (antigen-binding region, complement-binding region, constant part interacting with Fc receptors).



# Monoclonal Antibodies



Enbrel®  
Etanercept



Remicade®  
Infliximab



- **Infliximab is efficacious in Crohn's disease<sup>1)</sup>, but etanercept is not<sup>2)</sup>**



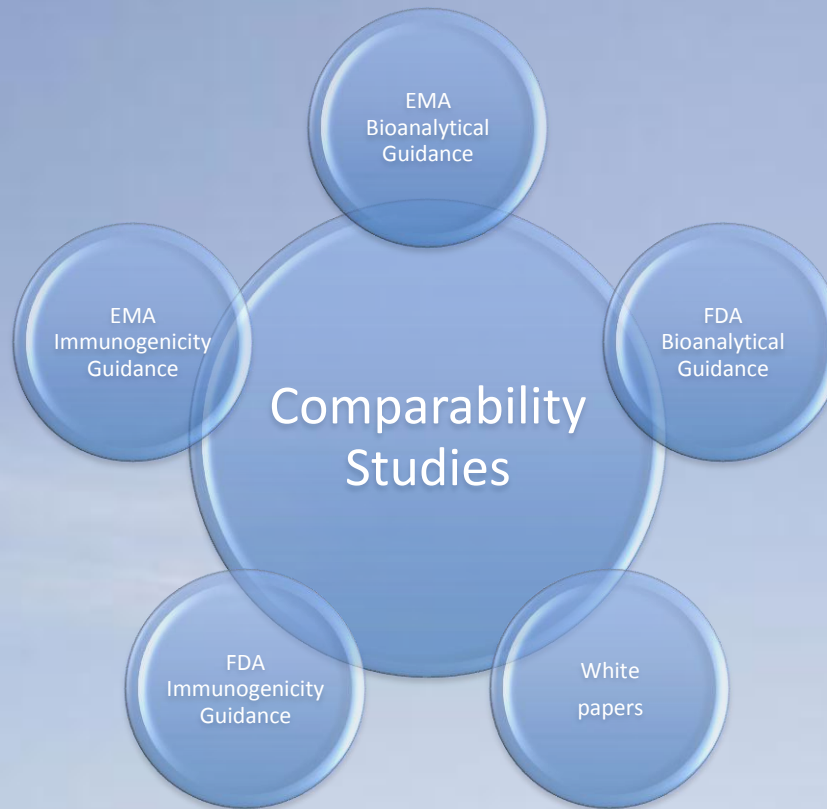
Christian K. Schneider

1) European Medicines Agency (EMA). European Public Assessment Report for Remicade. <http://www.emea.europa.eu/humandocs/Humans/EPAR/remicade/remicade.htm> (2007).

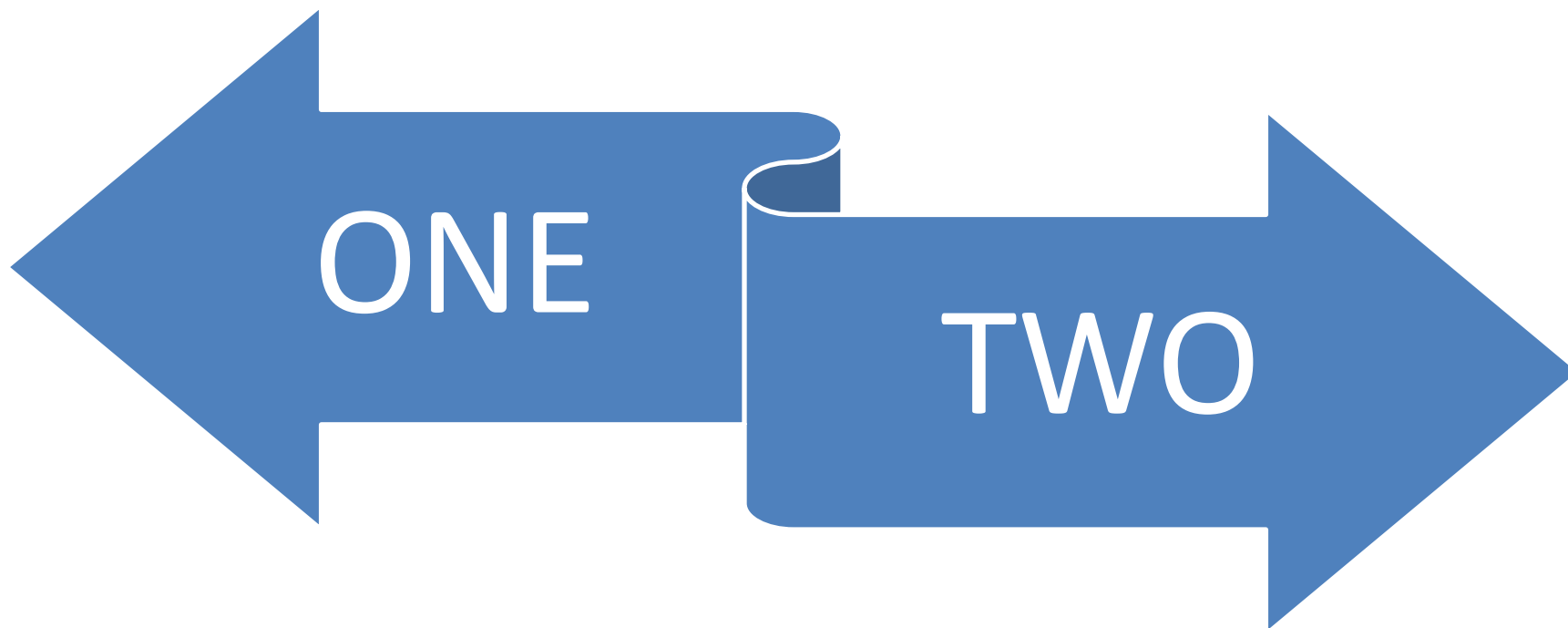
2) Sandborn, W.J. et al: Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 121(5):1088-94 (2001).



# Bioanalytical Testing (PK/TK and Immunogenicity testing) – Scientific and Regulatory Gap

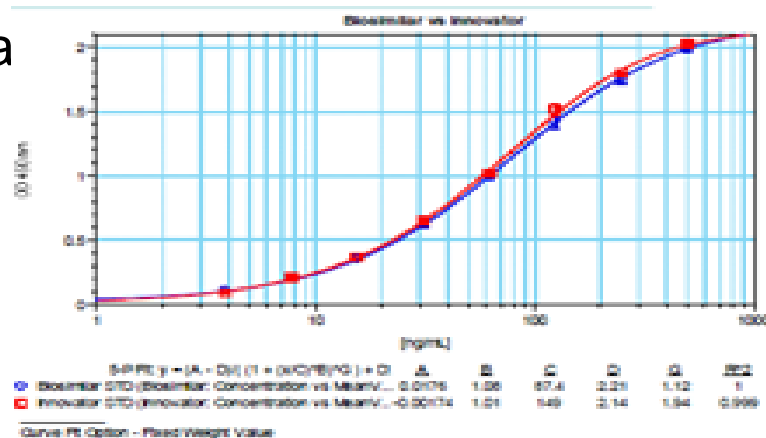


# Bioanalytical Testing (PK/TK Assay)



# Design of Bioanalytical Testing (One PK/ TK Assay)

- Standard curve: Innovator or Biosimilar
- QCs: Innovator and Biosimilar
- Custom reagents: Capture and detection antibodies generated against both innovator and biosimilar. Reagents should be well characterized and cross-verified. Celerion has observed greater than >30% differences between innovator and biosimilar due to differences in reagents.
- Assay parameters to be investigated
  - Accuracy and precision
  - Sensitivity
  - Selectivity
  - Specificity
  - Stability



**State of the art technology should be utilized for PK / TK assays**

# PK/TK Assay (Pre-study validation)

## Accuracy Precision

- **Innovator and Biosimilar QCs at same level**
- **+/- 20% RE and 20%CV (25% at LLOQ); Total error 30% (40% at LLOQ)**

## Selectivity

- **Innovator and Biosimilar**
- **80% of the matrices within 20% RE**

## Sensitivity

- **Innovator and Biosimilar**
- **25% recovery at LLOQ**

## Stability

- **Innovator and Biosimilar**
- **20% RE**

# PK/TK Assay (In-study validation)

## QCs

- **Innovator and Biosimilar QCs**
- **4-6-20 rule**

## Sample analysis

- **Ideally should be set up for simultaneous analysis of Biosimilar and Innovator**

## ISR

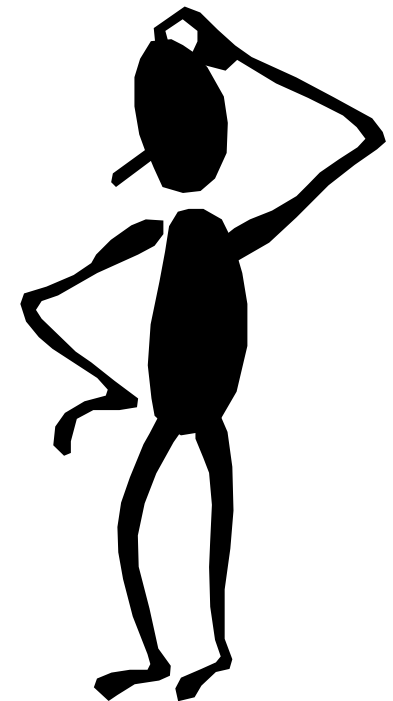
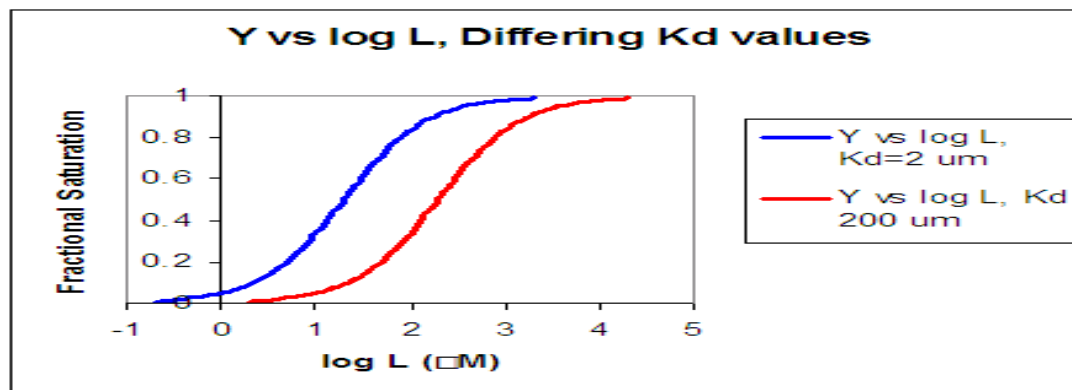
- **Perform ISR for both Innovator and Biosimilar**

## Stability

- **Samples (both Innovator and Biosimilar) should be within their respective stability period**

# Design of Bioanalytical Testing (Two PK/ TK Assay)

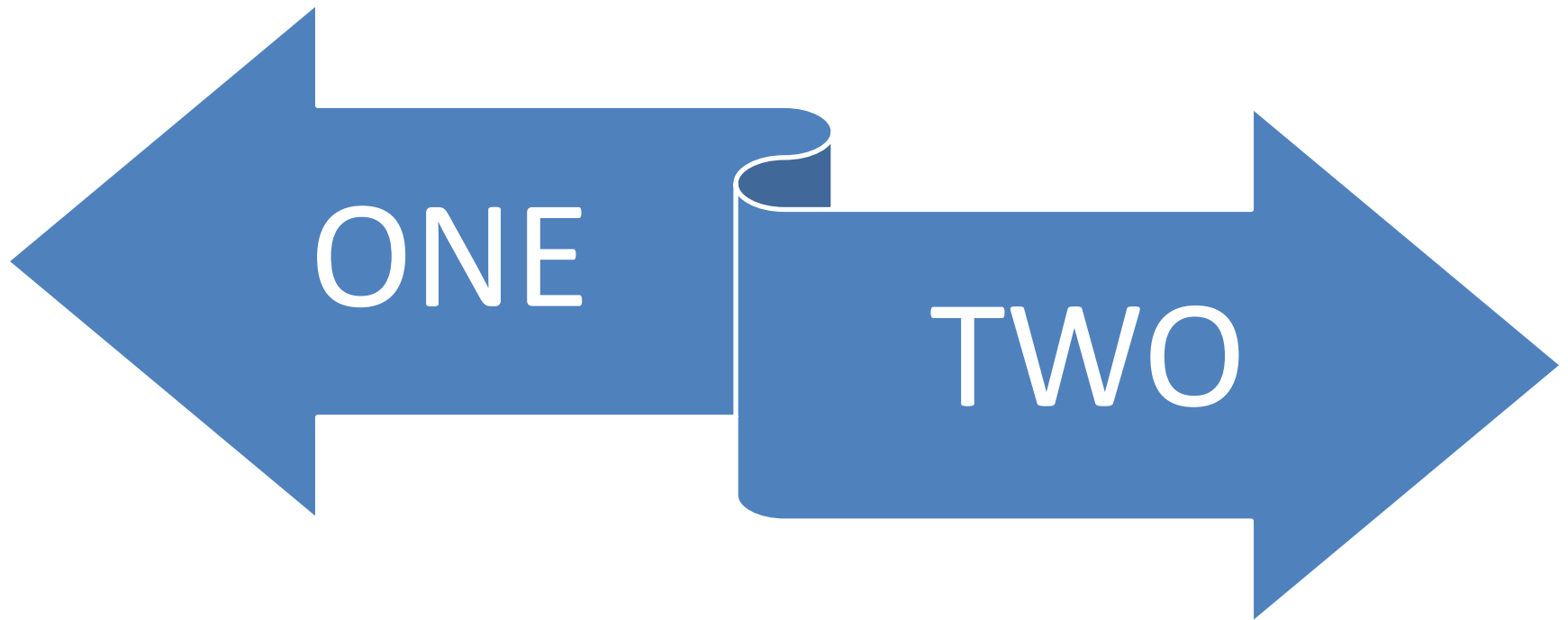
- If two assays are used (one for Biosimilar and one for Innovator):
  - Same platform?
  - Same sets of reagents?
  - Same assay conditions?
  - Cross-validation – use of correction factor
- Results:
  - Challenges in interpreting the results
  - Investigations - source of the differences
    - Reagents?
    - Platform?
    - Biosimilar is NOT similar?



# Bioanalytical Testing (PK/TK and Immunogenicity Assays) – Scientific and Regulatory GAP

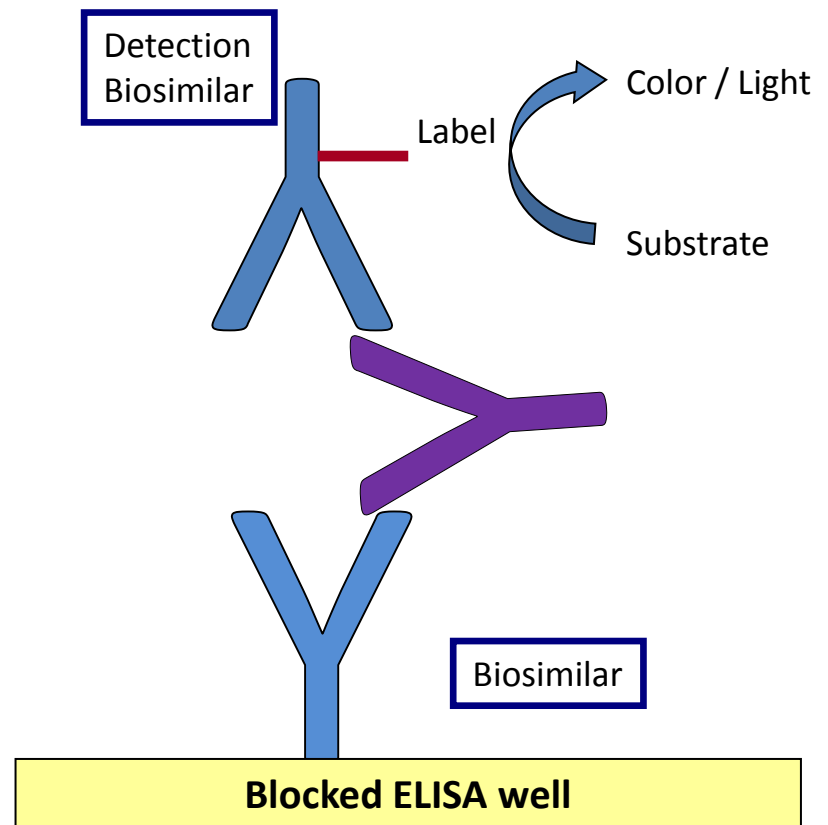
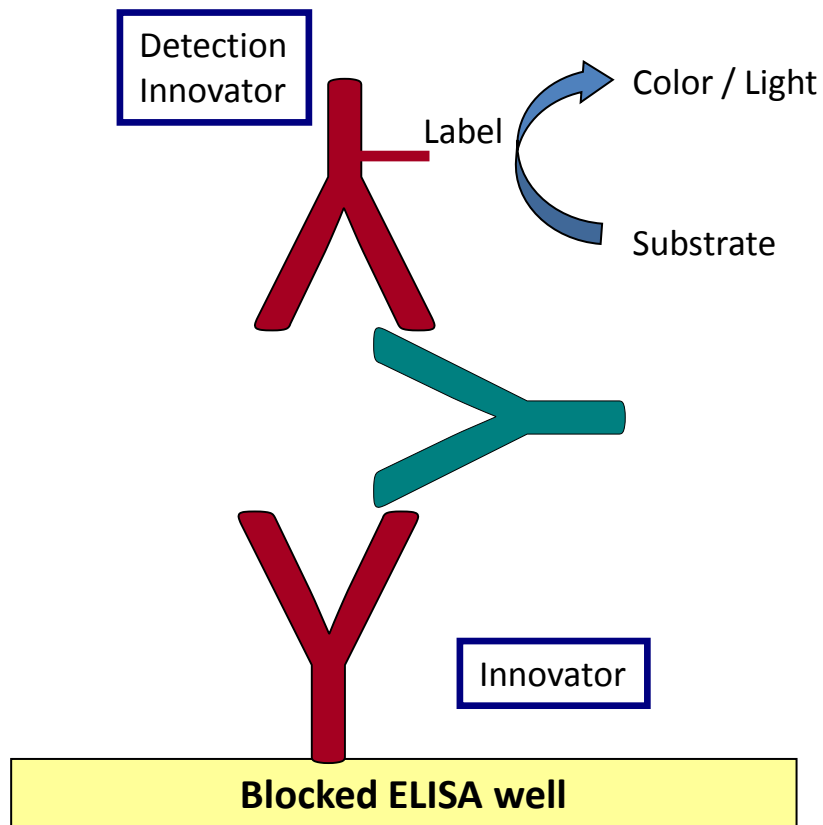


# Bioanalytical Testing (Immunogenicity Assay)

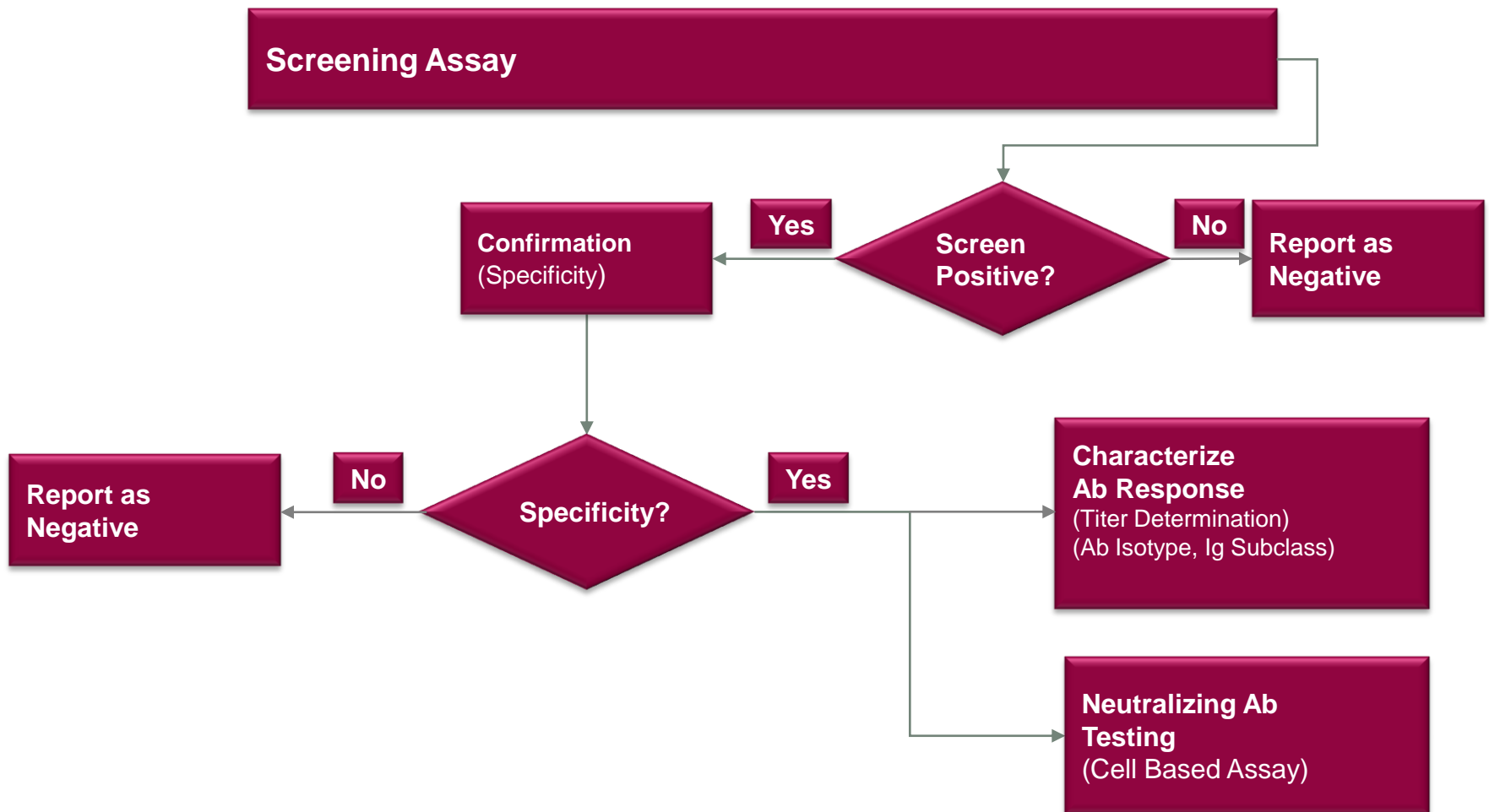




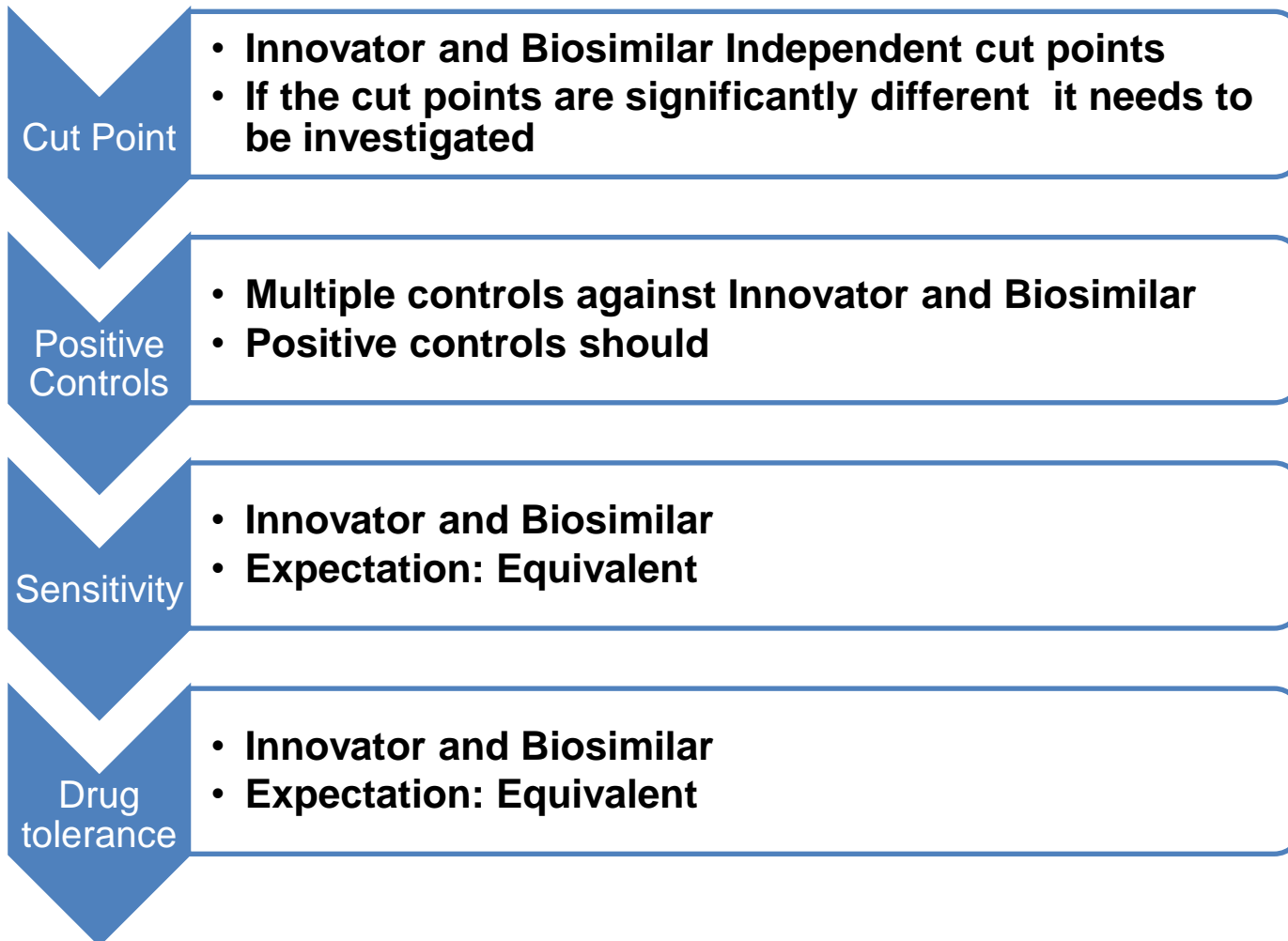
# Design of Bioanalytical Testing (Immunogenicity Assay)



# Typical Work Flow

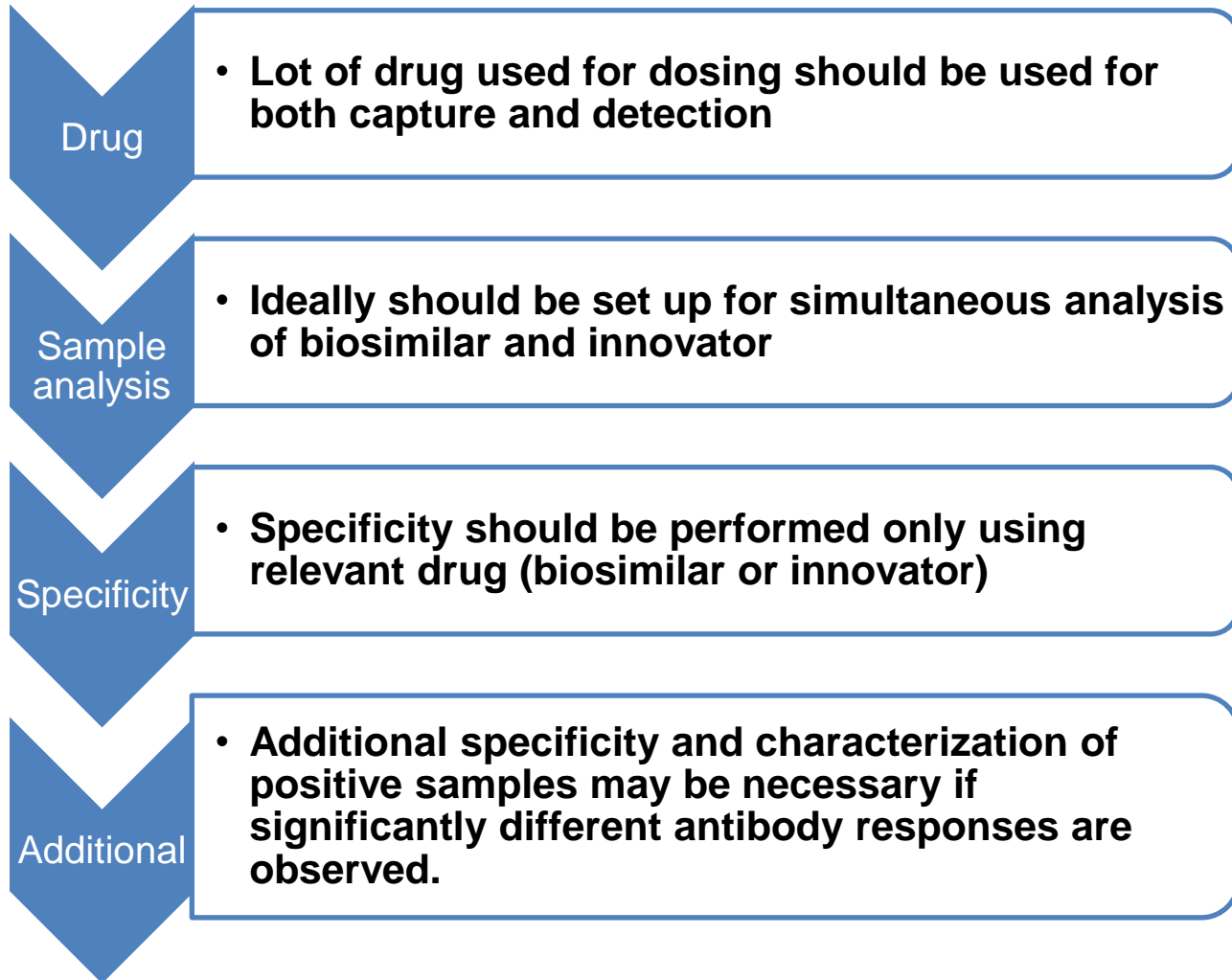


# Immunogenicity Assay (Pre-study validation)



**State of the art technology should be utilized for Immunogenicity assays**

# Immunogenicity Assay (In-study validation)



# Post-marketing surveillance of immunogenicity

- Post- marketing surveillance of immunogenicity key requirement all biosimilars
- Pre-market clinical testing of immunogenicity is limited and cannot reliably detect rare, but serious immunogenic responses
- Immunogenicity may be predictive of clinical consequences. It is important to understand potential mechanism(s) causing change and determine relevance
- Potential for conflict and confusion if patient treated with both reference and biosimilar products – which product elicited immunogenic response?
- Reference product sponsor and biosimilar firm will have different analytical methods for measuring immunogenicity and may report different results for the same patient samples

# Summary

- Monoclonal antibodies are complex molecules
- PK assay – one assay should be used to measure both innovator and biosimilar drug.
- Immunogenicity assay – two assays should be used to measure anti-drug (innovator and biosimilar) antibodies.
- A robust assay is required to monitor long term immunogenicity assessment.
- Interpretation of results (establishment of biosimilarity) is challenging ; specifically when working with a qualitative immunogenicity assays
- State of the art technologies should be used for both PK and Immunogenicity assays

# The Celerion Solution



The bridge between  
manufacturing and clinical efficacy

