Quality-focused Development Strategy of Biosimilar Product

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Outline

PART I	Quality-focused Analytical Assessment
PART II	Heterogeneity of Biologic Product
PART III	Similarity Assessment
PART IV	Closing Remarks

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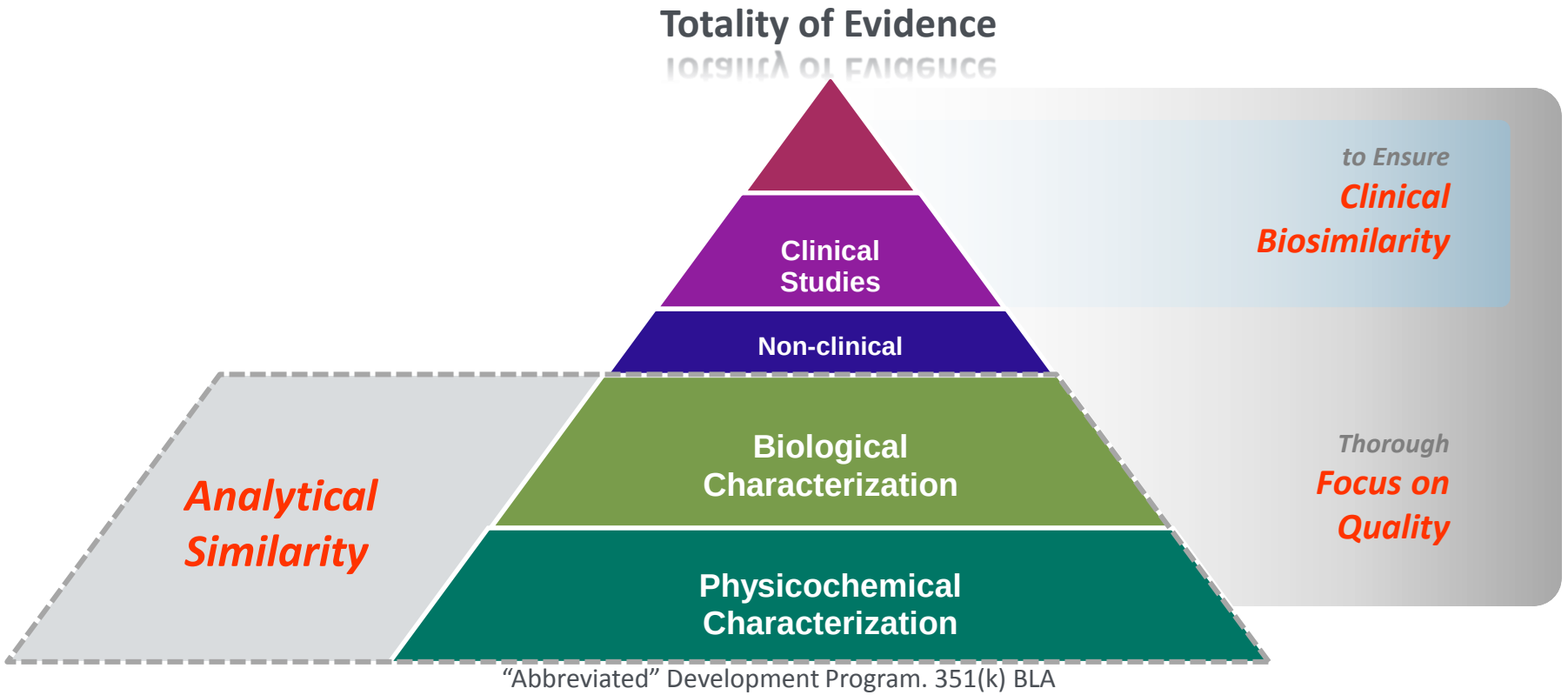
PART I

Quality-focused Analytical Assessment

Quality Based Biosimilar Development Strategy

- **Science-based quality evaluations maximize clinical biosimilarity.**
- **Stepwise assessment begins with extensive structural and functional characterization of the reference product and the biosimilar.**

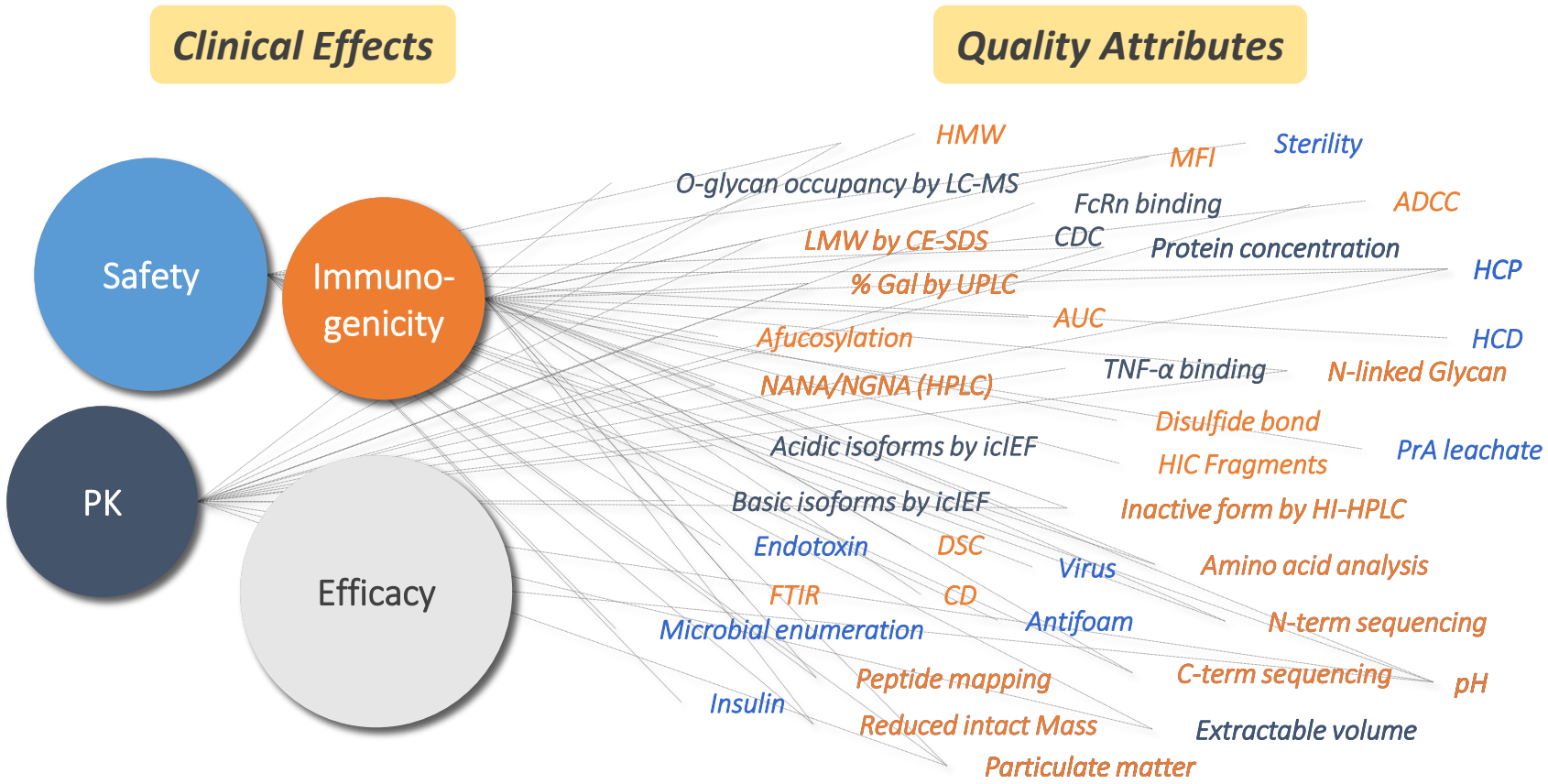


"Abbreviated" Development Program. 351(k) BLA

US Health and Human Services, Food and Drug Administration. Guidance for industry, clinical pharmacology data to support a demonstration of biosimilarity to a reference product. Rockville (MD): FDA; 2016 Dec.

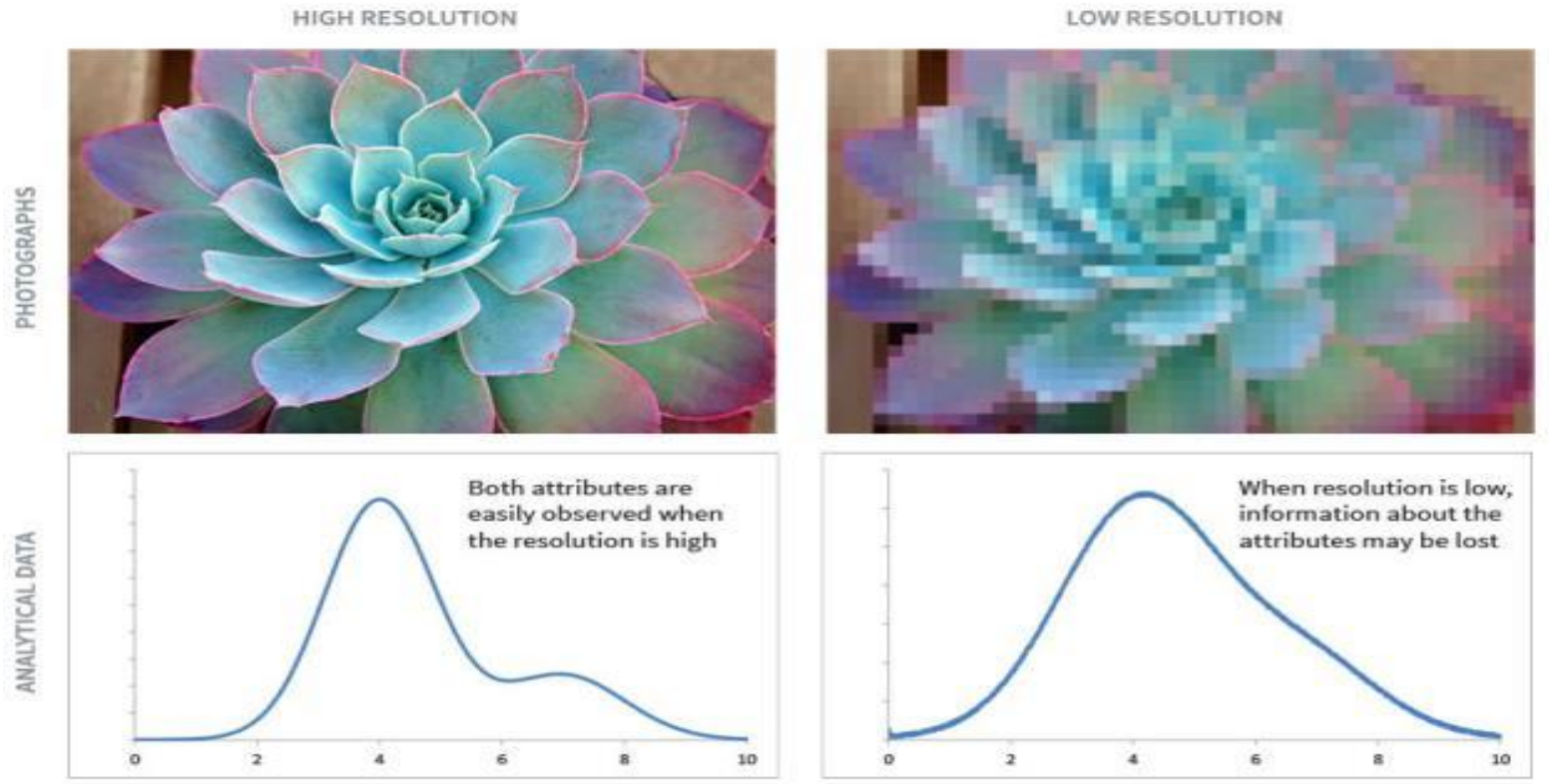
Characterization as the Foundation

- **Comparing products using a analysis algorithm that covers a large number of product quality attributes with highly sensitive, orthogonal methods ensures similarity of clinical outcome**



Importance of Analytical Method Sensitivity

- **Sensitivity of analytical method is important for similarity assessment**



Mass spectrometry example

Year	Detecion limit for peptides (pmol)
1990	100
1993	10
1997	1
2000	0.1
2003	0.01
2005	0.001
2008	0.0001
2011	0.00001

10 million-fold increase

Adapted from a presentation by Anthony Mire-Sluis, 9th Symposium on the Practical applications of Mass Spectrometry in the Biotechnology Industry (mass Spec 2012); 11-14 September,2012, San Diego, CA, USA.

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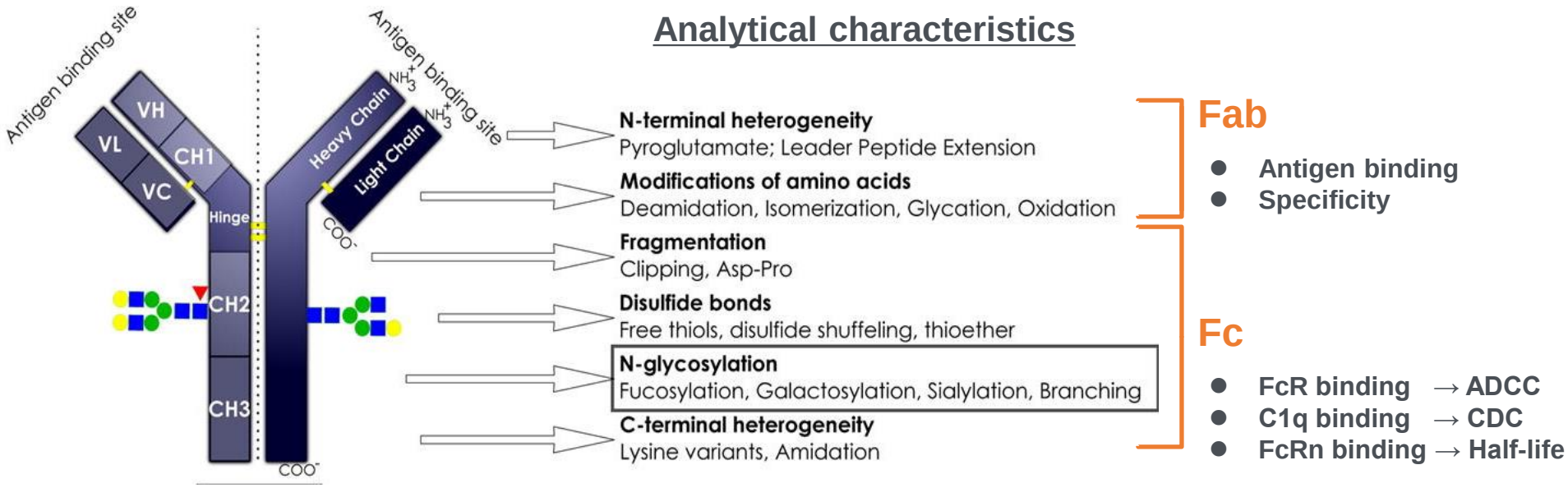
PART II

Heterogeneity of Biologic Product

Monoclonal Antibodies as the Biosimilar

- **Monoclonal antibodies are complex molecules.**
  - Post-translational modifications
- **Mode of action is complex and may involve contributions from multiple mechanisms.**
  - Need to consider the correlation of functional activities with physicochemical results or with the results for preclinical and clinical studies

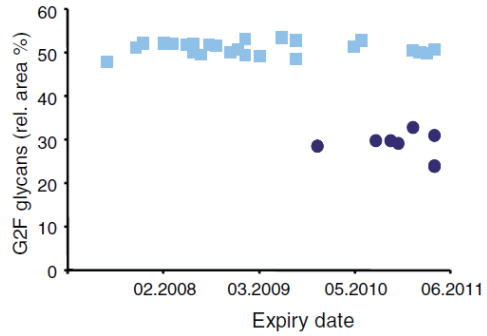


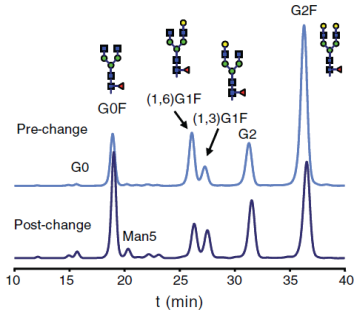
Higel F et al. European Journal of Pharmaceutics and Biopharmaceutics 100 (2016) 94–100

Heterogeneity for Quality Attribute in Biologics

Reference etanercept

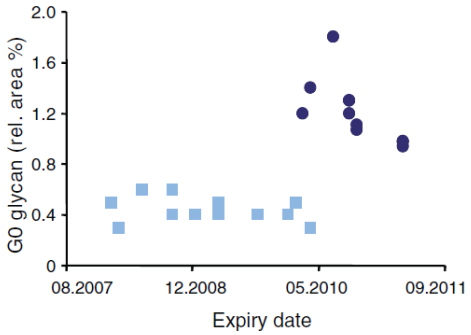
- Two distinct glycosylation profiles in some of later batches (after 2009)

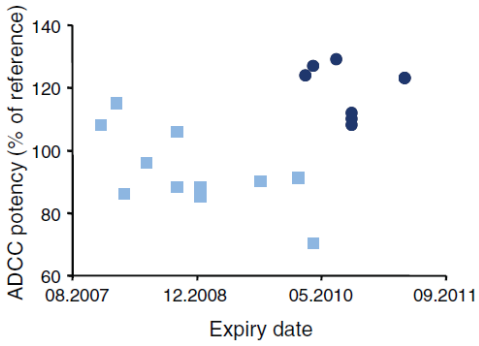




Reference rituximab

- Higher unfucosylated glycans (G0) and ADCC in some of later batches (after 2010)



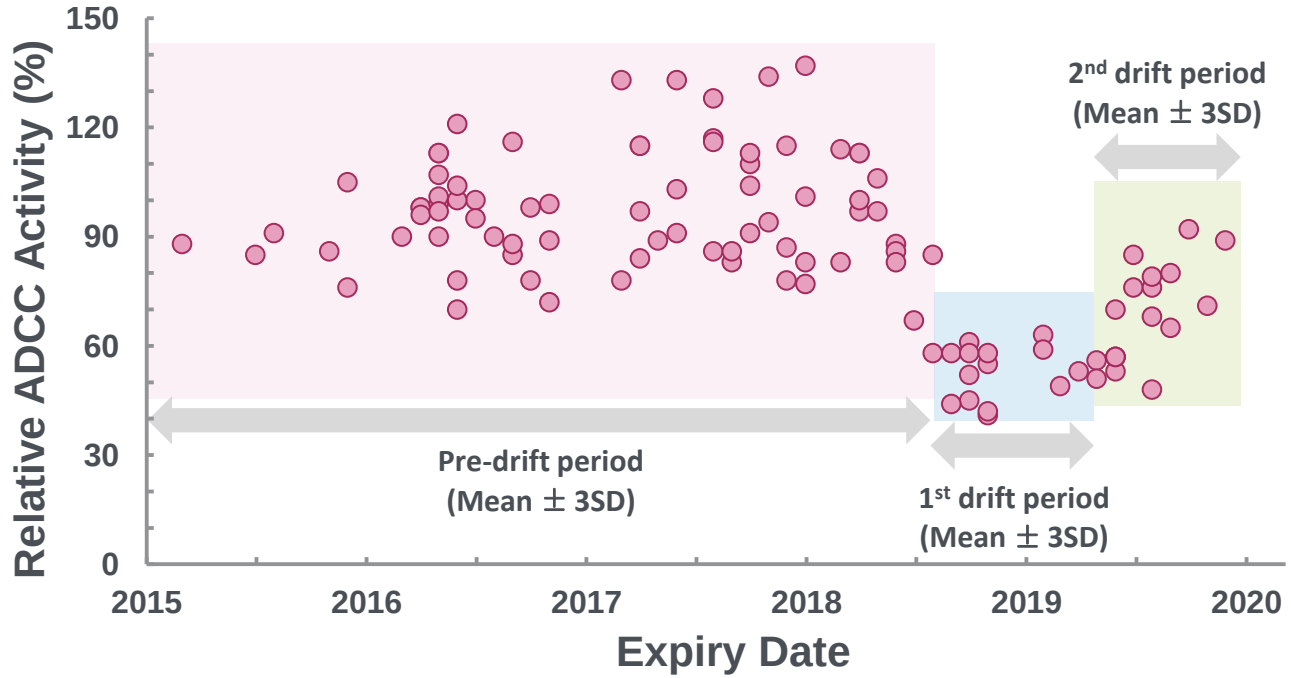


Schiestl M, et al. Acceptable changes in quality attributes of glycosylated biopharmaceuticals, Nature Biotechnology (2011) 29:310-312

Heterogeneity for Quality Attribute in Biologics

Reference trastuzumab

- **ADCC activity showed 2 marked drifts.**
  - 1st drift: A marked downward drift in %afucose
  - 2nd drift: An upward drift in %high mannose



Kim S, et al. Drifts in ADCC-related quality attributes of Herceptin : Impact on development of a trastuzumab biosimilar, mAbs (2017) 9(4):704-714

Heterogeneity Risk Mitigation

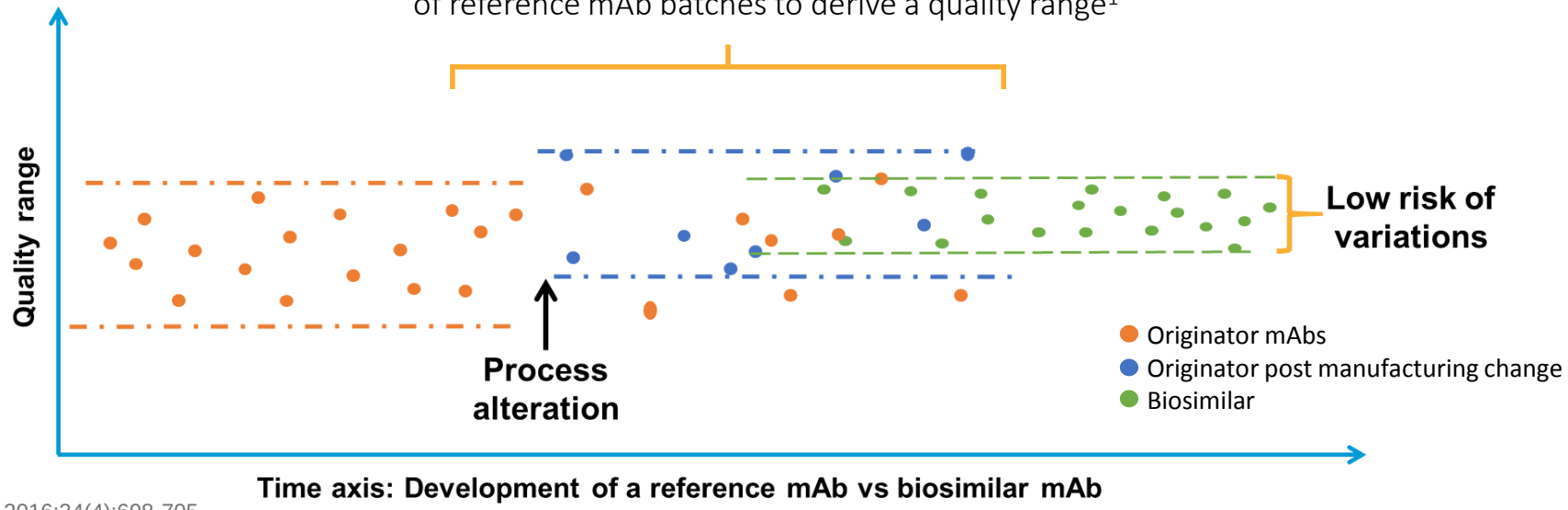
Sample As Many As Possible, As Long As Possible

- Characterize multiple lots of reference (Innovator) product

Define a Quality Target Range for the Biosimilarity Assessment

- Monitor throughout the entire biosimilar development period

Biosimilar mAb has to take in consideration of the largest historical data of reference mAb batches to derive a quality range[1]



[1] Gonçalves J, et al. Clin Exp Rheumatol 2016;34(4):698-705

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PART III

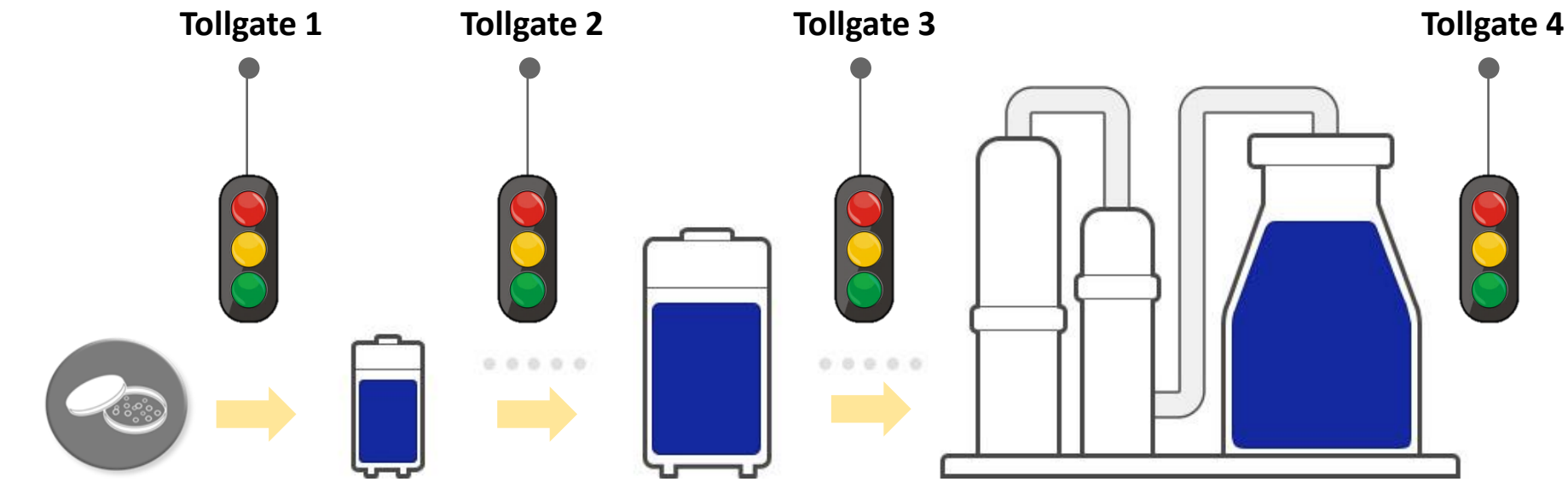
Similarity Assessment

Tollgate System for Similarity Assessment

- **Tollgate system ensures high quality biosimilar development.**

Similarity Assessment

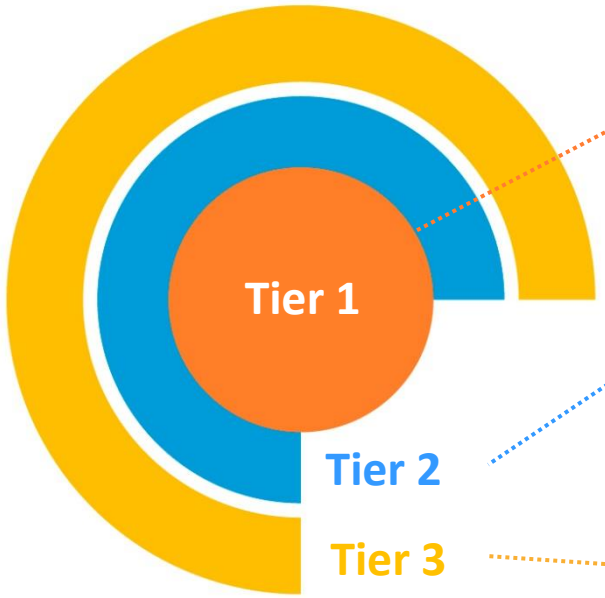
Establish stringent quality goals for a go/no go decision at key development steps



Tiering of Quality Attributes

- **Each similarity assessment was designated to a tier based on the clinical relevance of the attribute.**

Analytical Similarity Assessments by Risk-based Assessment
(Case of SB3, a Herceptin® Biosimilar Candidate)



- Inhibition of cell proliferation
- Antibody-dependent cellular cytotoxicity (ADCC)

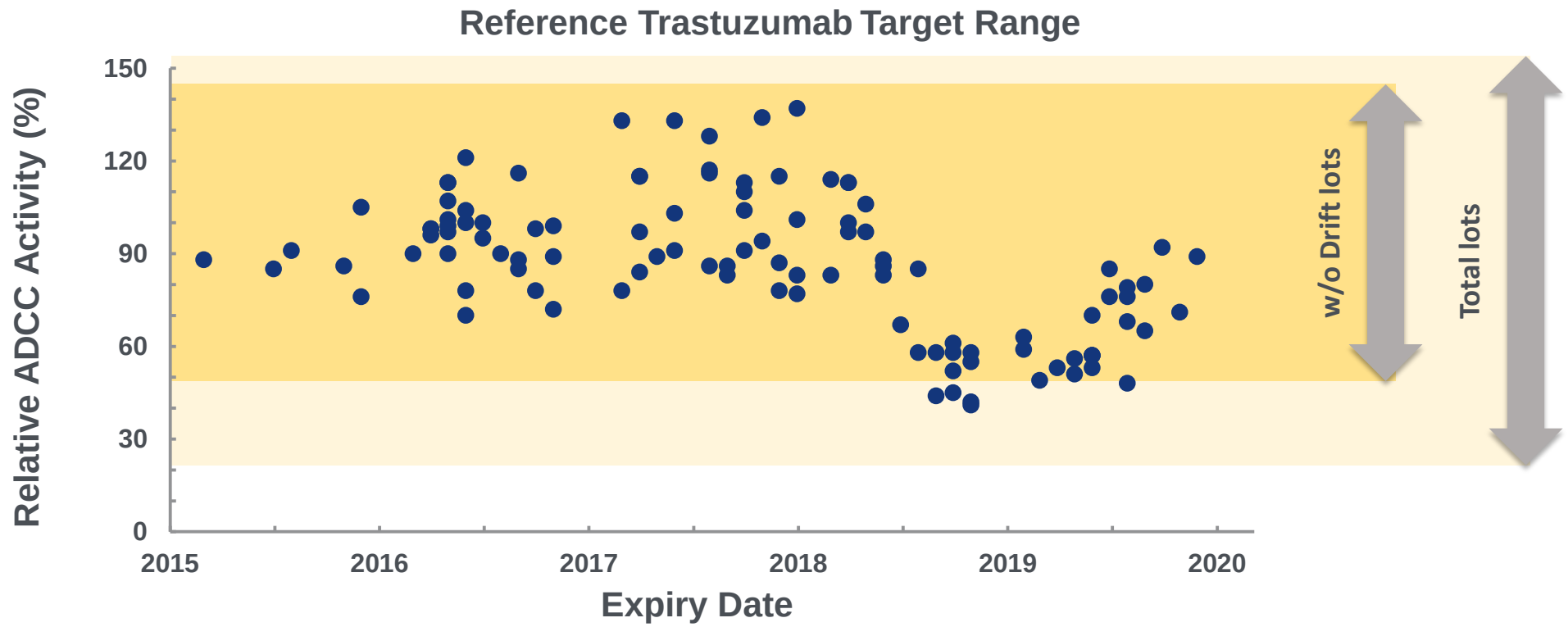
- HER2 binding
- FcγRIIIa binding
- FcRn binding
- C1q binding
- Purity
- Glycosylation
- Charge variant

- Fc Receptor binding
- *In vitro* angiogenesis
- Surface HER2 level
- HER2 ECD shedding
- Akt phosphorylation
- Combination with chemotherapy
- Antibody-dependent cellular phagocytosis (ADCP)

.[1] Data on file; Samsung Bioepis Co., Ltd

Similarity Range Set-up: Case study

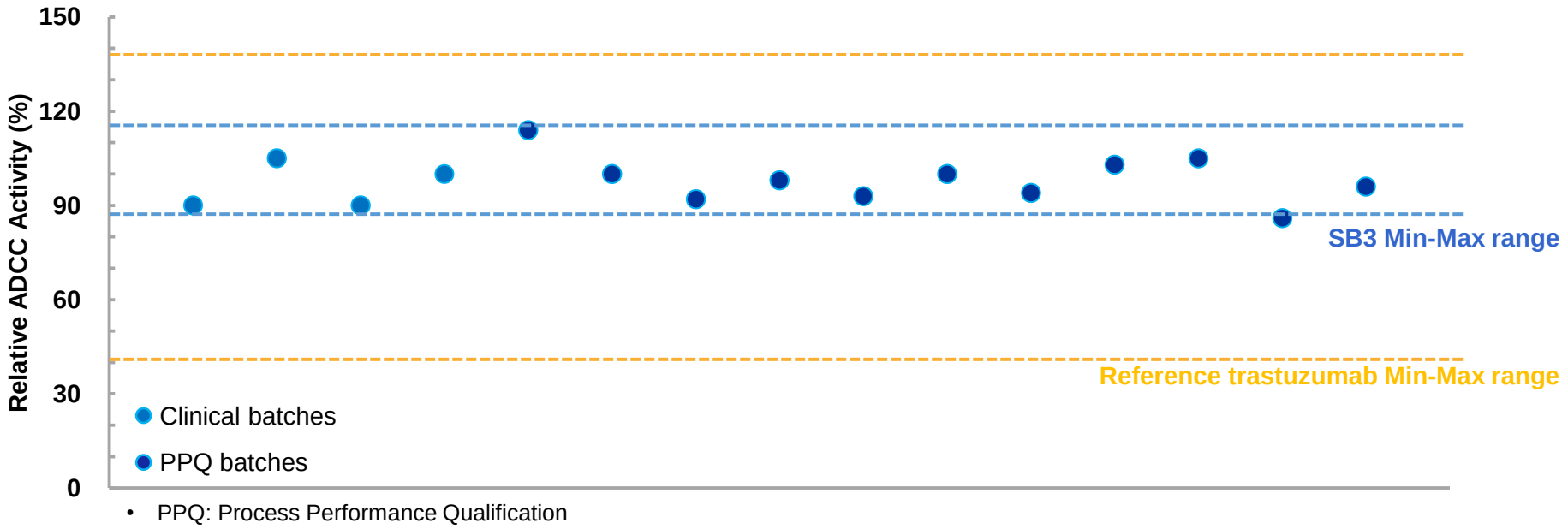
- **Quality Target Range was defined for the biosimilarity assessment**
  - Reference product has been monitored throughout the entire biosimilar development period.
  - 146 lots of reference trastuzumab were analyzed for setting the similarity range.



Data on file

Quality Management of SB3

- **ADCC activity of SB3 showed high consistency.**

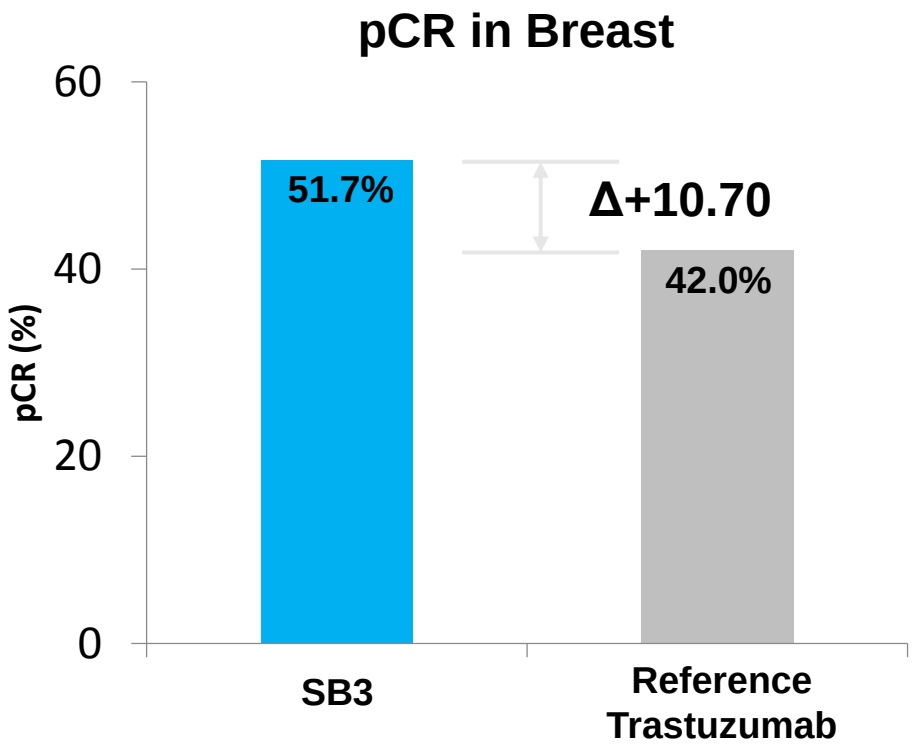


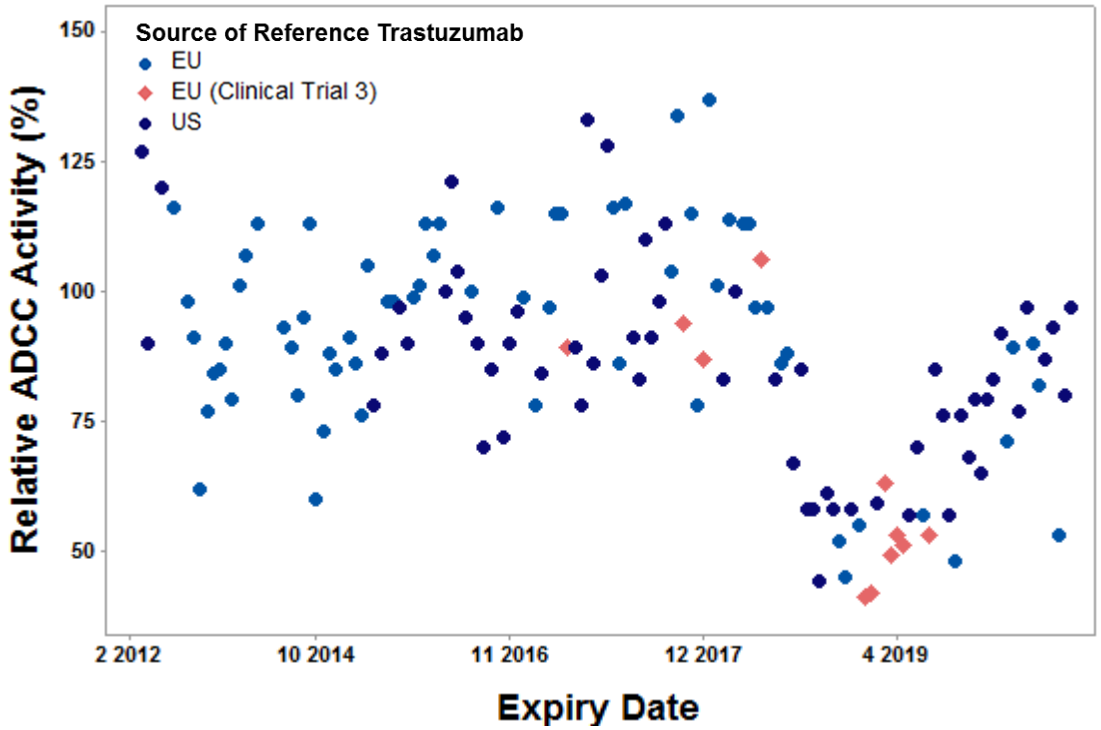
- PPQ: Process Performance Qualification

Data on file

Clinical Efficacy of SB3

- **pCR in breast at primary endpoint was not inferior to reference trastuzumab.**
  - Slightly above the upper end of pre-defined equivalence margin
  - Consider for shift of ADCC activity for some reference trastuzumab batches used for clinical trial





Adjusted difference **10.70%** (95% CI, 4.13, 17.26)
Adjusted ratio 1.259 (90% CI, 1.112, 1.426)

a Pivot X, et al. J Clin Oncol 2018 :JCO2017740126 [Epub ahead of print]
b Data on file

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PART IV

Closing Remarks

Summary

Striving to develop methods that can determine analytical similarity is an important step in biosimilar characterization.

Biologics have inherent structural complexity and modifications.

Quality control is critical for identifying changes in the reference product quality profile that can impact development.

Monitoring similarity against the quality target range throughout the product lifecycle ensures a continuous focus on quality throughout biosimilar development.

Tight quality management of biosimilar product ensures biosimilarity to the originator product.