The impact of biosimilar quality for clinical safety and efficacy: the case of Trastuzumab

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Disclosures

Research Collaboration Projects:

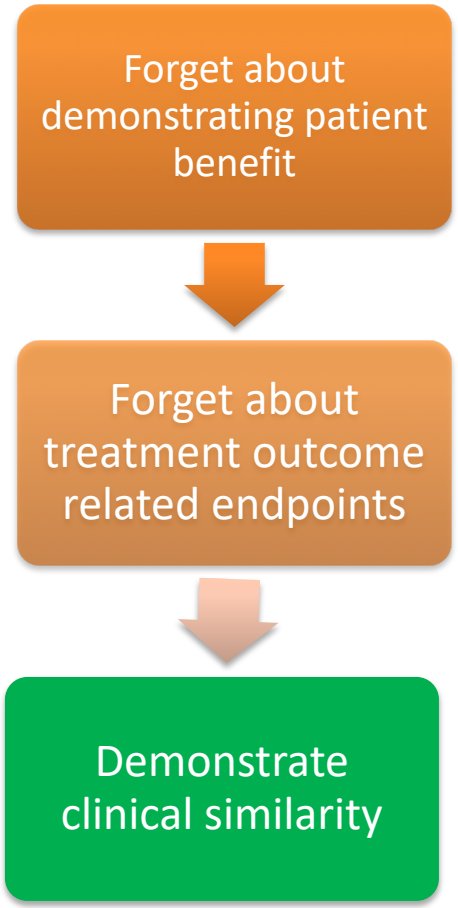
- Shire
- Janssen
- Merck (MSD)
- Pfizer
- TechnoPhage

Consultancy:

- EMA/Infarmed
- MSD
- Sandoz
- Abbvie
- Hikma
- Samsung Bioepis
- Roche
- Pfizer
- Celltrion
- Biogen

This presentation reflects my personal assessment

Biosimilars:
The Paradigm Shift from the Patient to the Drug



Think about the drug

(PK,PD, Immunogenicity)

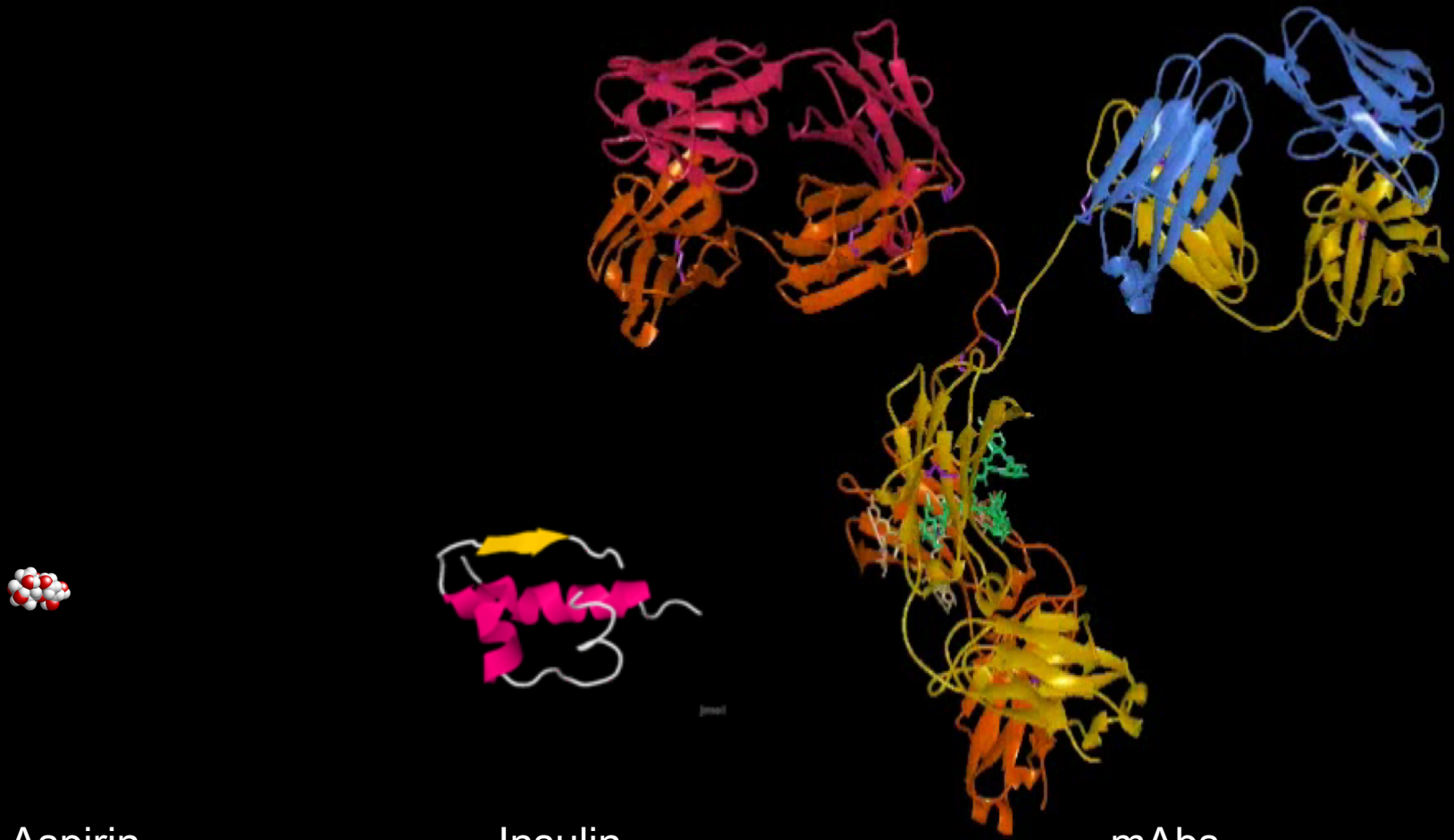
Change of scenario with Oncology Biosimilars arriving in EU

- Many oncology biosimilars are currently in development, with the first monoclonal antibody biosimilar approved for an oncologic indication (a rituximab biosimilar) by European Medicines Agency (EMA) in 2017. [1,2]
- Multiple trastuzumab biosimilars are under regulatory review[1,2]

Active Substance	Number in Development[1]	Number Approved by EMA[2]
Trastuzumab	5	1
Bevacizumab	6	1
Rituximab	5	2

1. EMA, Biosimilar Medicines (https://www.clinicaltrialsregister.eu/); Accessed 01/08/2017 (phase 3). 2. ClinicalTrials.gov; Accessed 01/08/2017.

Relative complexity of biologic agents



Aspirin

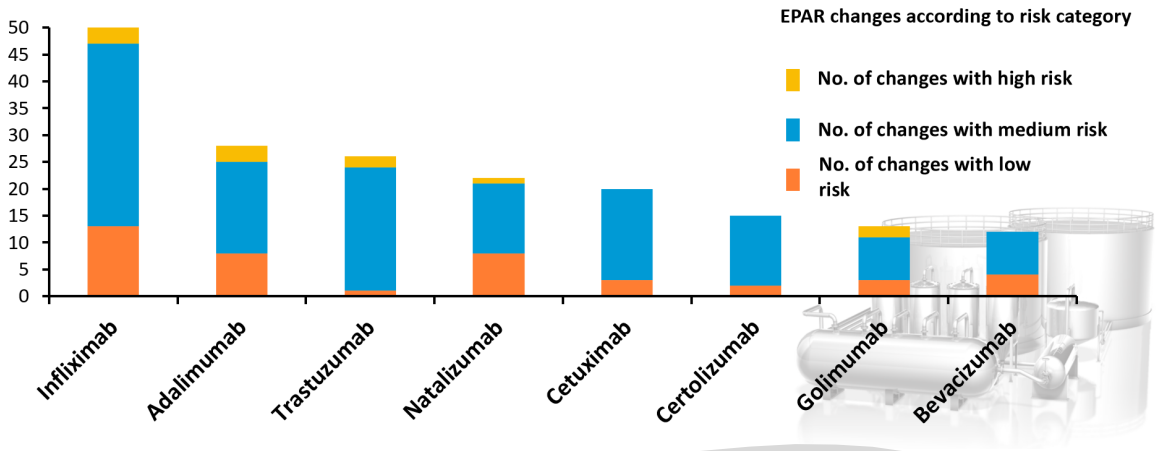
Insulin

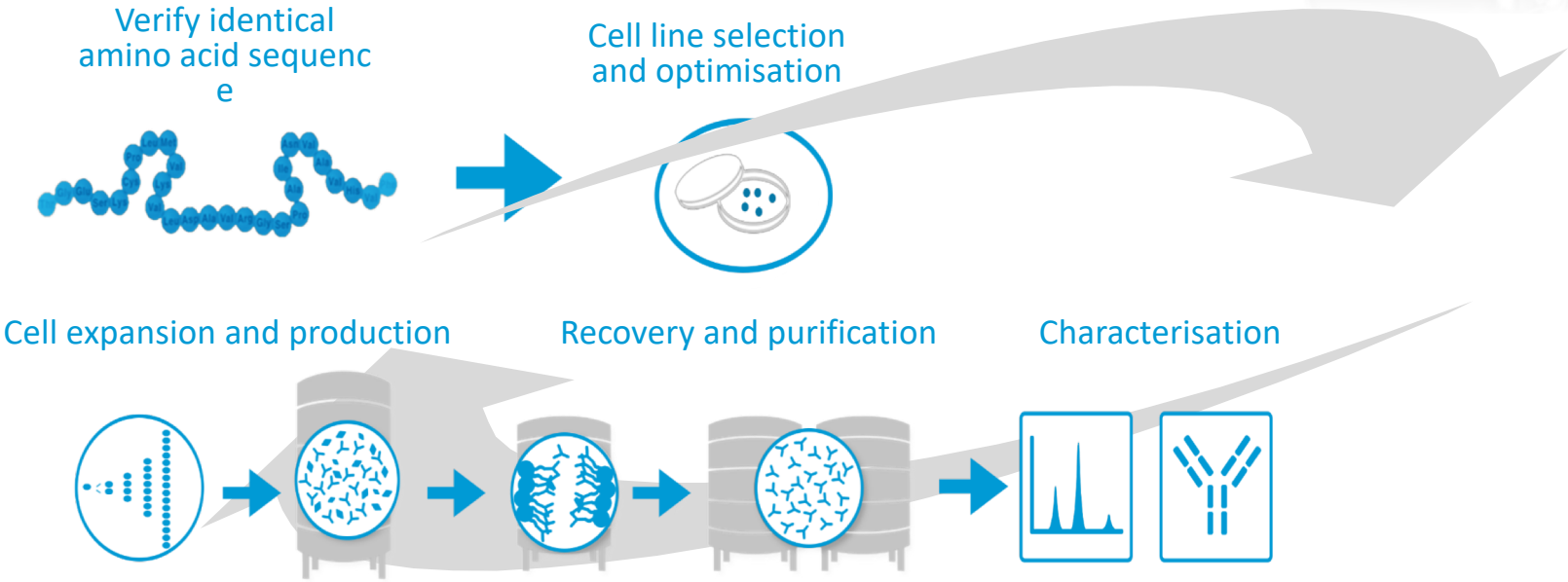
mAbs

Biopharmaceutical Process Modification and Variability of Biologics

Changes of manufacturing must be shown to have no impact on the identity, purity, potency, quality, and safety of product[1]

Manufacturing Changes of Original Biologics[1]



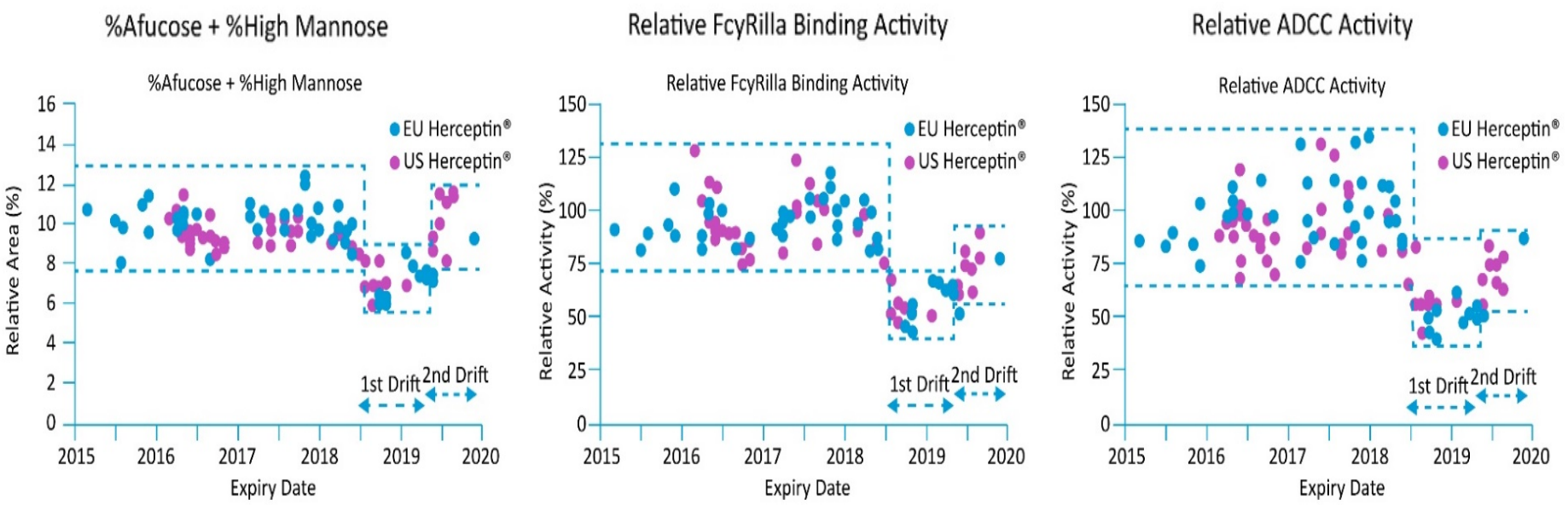


1. Vezér B, *et al. Curr Med Res Opin* 2016;32:829–834.

Change in Quality Profile of original trastuzumab

- Quality attributes were continuously monitored over 5 years by analyses of dozens of lots of EU- or US-marketed original biologic[1]
- Changes in glycosylation, Fc receptor binding, and ADCC activity were observed in lots manufactured during a select period of time[1]

Drift in Glycosylation, Fc Receptor binding, and ADCC of Herceptin® batches



1. Kim S, *et al*. *Mabs* 2017;9(4):704–714.

Manufacturing process changes are regulated by international guidelines and are distinct from demonstrating biosimilarity

Manufacturing process change for an approved biologic medicine

Manufacturers need to demonstrate that any change does not adversely alter clinical safety or efficacy, and they do so by utilising a "comparability exercise"

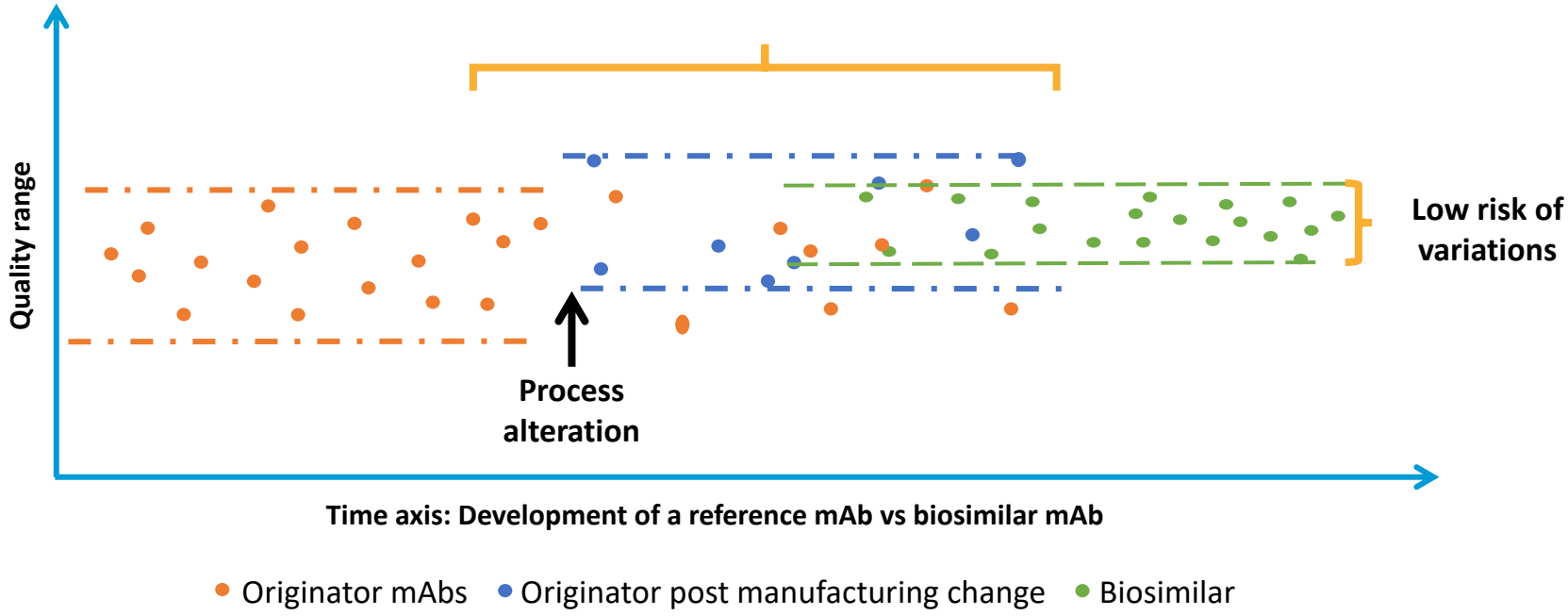
Depending on the magnitude of change, comparative pre- and post-change nonclinical and clinical data may be required (per ICH Q5E)

ICH Harmonised Tripartite Guideline, Comparability of biotechnological/biological products subject to changes in their manufacturing process Q5E, 2004

The Goal Posts of Biosimilarity: the Originator Sets the Rules for Quality

Can be more than 200 variables

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



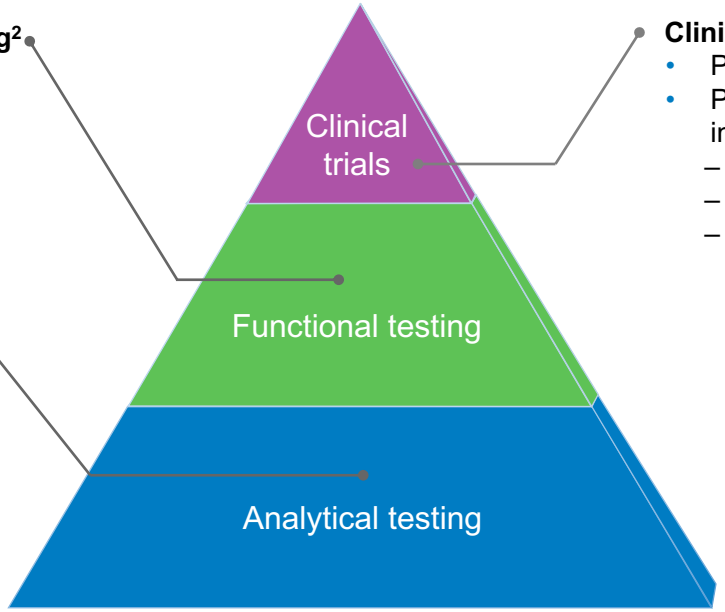
1. Gonçalves J, *et al. Clin Exp Rheumatol* 2016;34(4):698-705.

Rigorous preclinical testing is performed as part of the "totality of the evidence" approach

Biosimilar development[1]

***In vitro* binding and potency, eg[2]**
- TNFα binding
- TNFα neutralization
- Fc receptor binding
- C1q binding
- ADCC
- CDC

Structure, purity, and biochemistry[2]
- Primary structure
- Higher-order structure
- Purity/impurity
- Charged isoforms
- Glycosylation

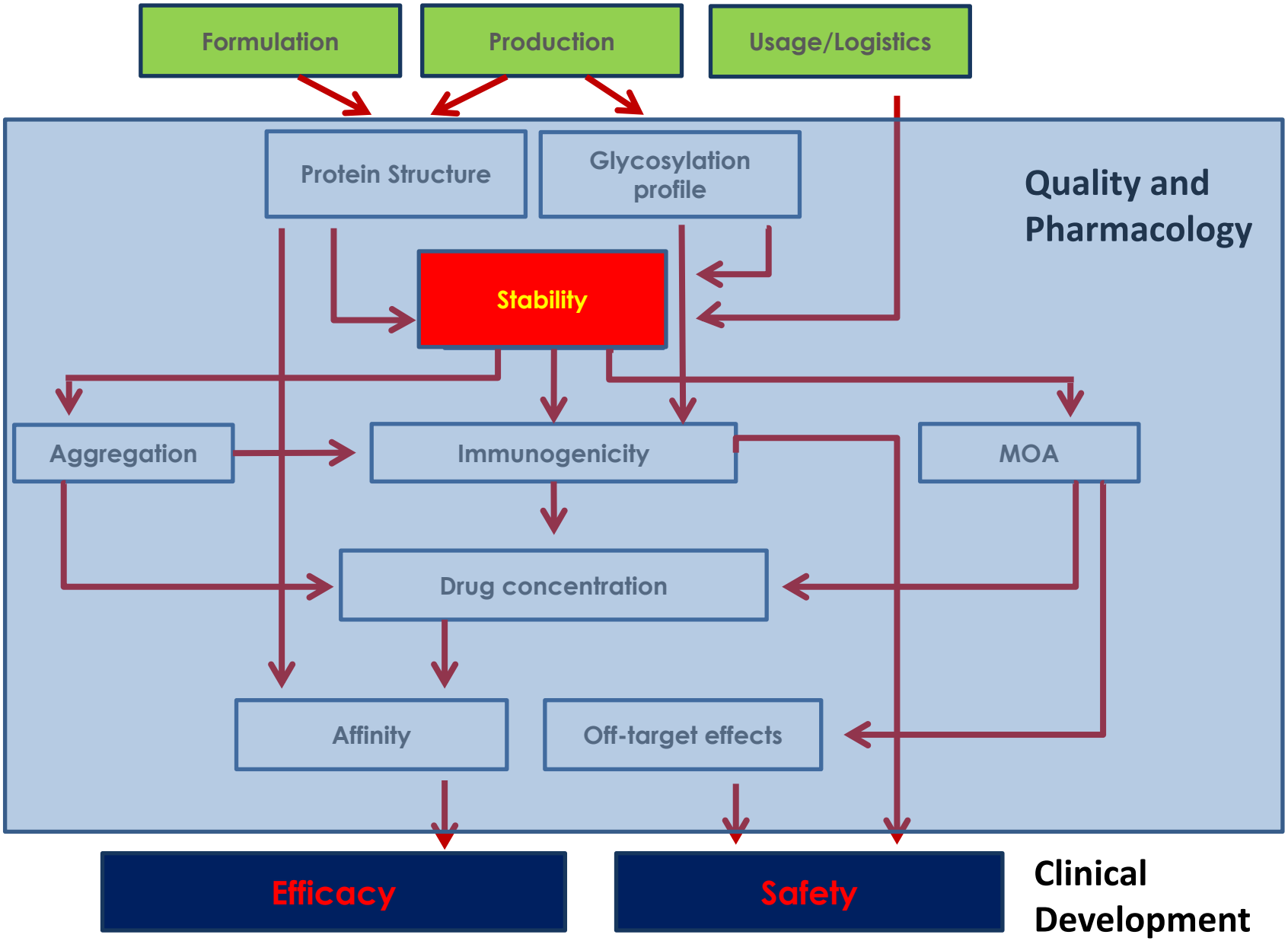


Clinical data[3]
- Phase I pharmacokinetics and safety
- Phase III equivalence trial in one indication
  - Efficacy
  - Safety
  - Immunogenicity

1. FDA. Quality considerations in demonstrating biosimilarity of a therapeutic protein product to a reference protein product. Guidance for industry, 2015;
2. EMA. Guideline on similar biological medicinal products, 2014;
3. FDA. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry, 2015.

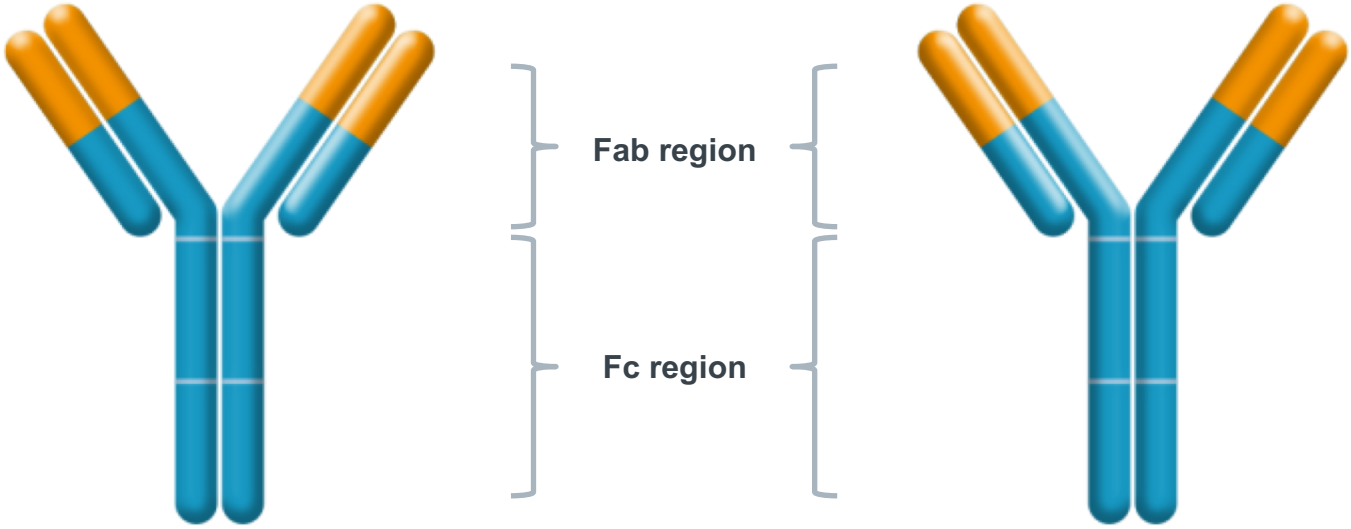
ADCC, antibody-dependent cell-mediated cytotoxicity;
C1q, complement factor 1q;
CDC, complement-dependent cytotoxicity;
Fc, fragment crystallizable;
TNFα, tumor necrosis factor α.

The Clinical Relevance of Critical Quality Attributes



Goncalves et al, 2013

Identical Amino Acid Sequence: Trastuzumab vs Originator Trastuzumab



Amino Acid Sequence of Originator Trastuzumab

Heavy Chain of Originator Infliximab

001 EVKLEESGGG LVQPGGSMKL SCVASGFIFS NHWMNWVRQS PEKGLEWVAE IRSKSINSAT 060
061 HYAESVKGRF TISRDDSKSA VYLQMTDLRT EDTGVYYCSR NYYGSTYDYW GQGTTLTVSS 120
121 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 180
181 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG 240
241 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN 300
301 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE 360
361 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 420
421 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 450

Light Chain of Originator Infliximab

001 DILLTQSPAI LSVSPGERVS FSCRASQFVG SSIHWYQQRT NGSPRLLIKY ASESMSGIPS 060
061 RFSGSGSGTD FTLSINTVES EDIADYYCQQ SHSWPFTFGS GTNLEVKRTV AAPSVFIFPP 120
121 SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT 180
181 LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC 214

Amino Acid Sequence of Trastuzumab

Heavy Chain of Remsima

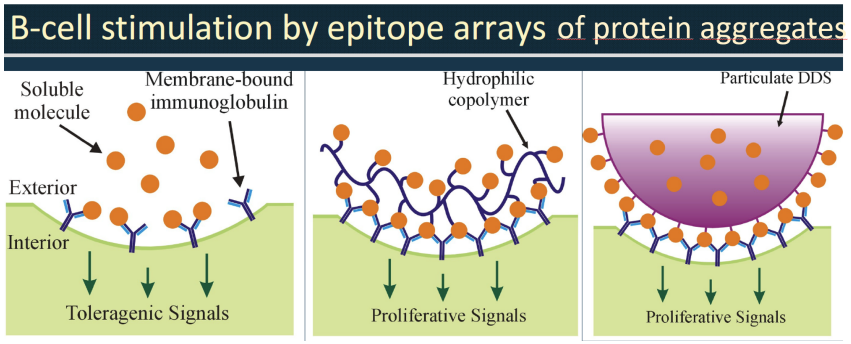
001 EVKLEESGGG LVQPGGSMKL SCVASGFIFS NHWMNWVRQS PEKGLEWVAE IRSKSINSAT 060
061 HYAESVKGRF TISRDDSKSA VYLQMTDLRT EDTGVYYCSR NYYGSTYDYW GQGTTLTVSS 120
121 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 180
181 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG 240
241 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN 300
301 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE 360
361 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 420
421 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 450

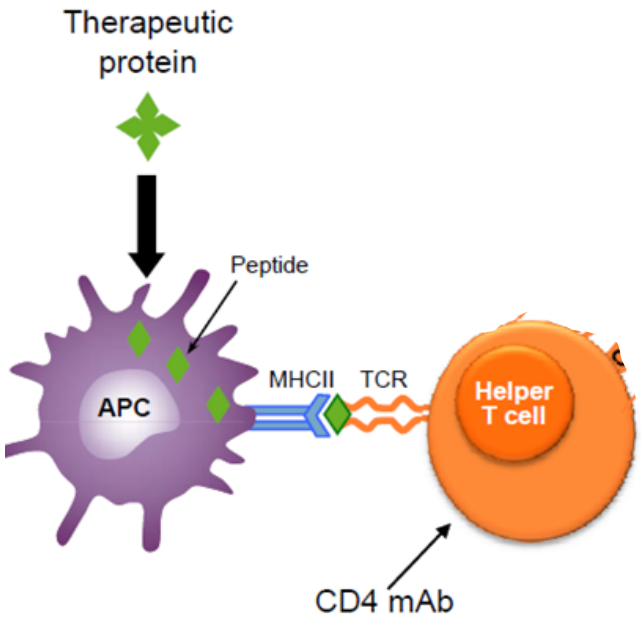
Light Chain of Remsima

001 DILLTQSPAI LSVSPGERVS FSCRASQFVG SSIHWYQQRT NGSPRLLIKY ASESMSGIPS 060
061 RFSGSGSGTD FTLSINTVES EDIADYYCQQ SHSWPFTFGS GTNLEVKRTV AAPSVFIFPP 120
121 SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT 180
181 LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC 214

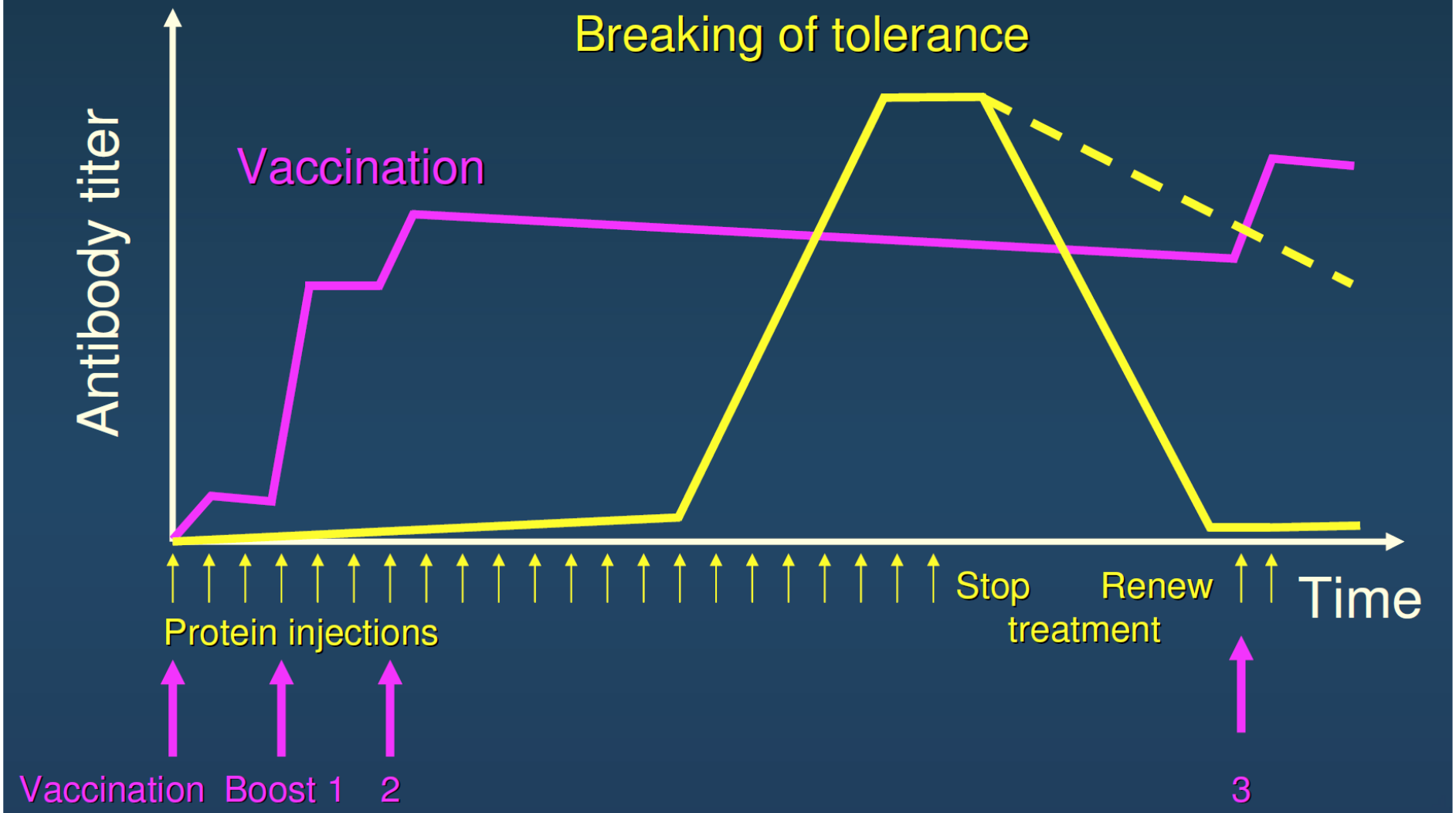
For illustrative purposes only.
Fab, fragment antigen-binding; **Fc**, fragment crystallizable.

The amplification of anti-drug immune responses





Classical immune response versus breaking of immune tolerance

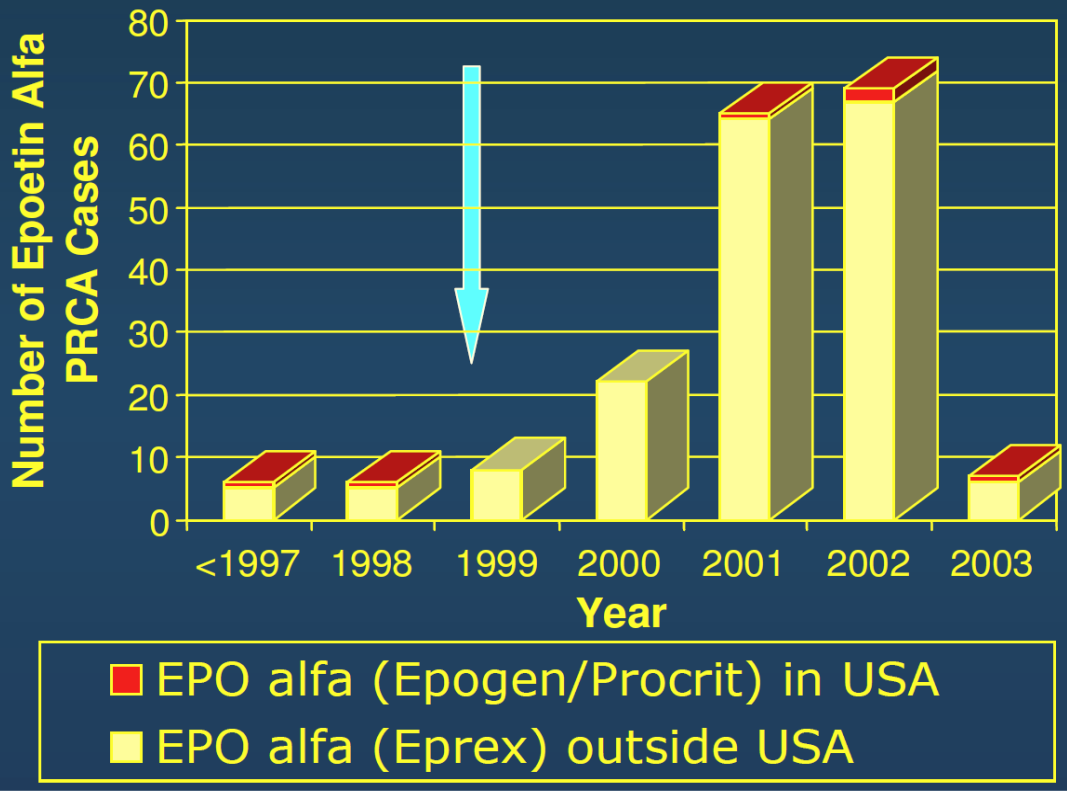


Immunogenicity against biologics: The quality matters

Anti-epoetin antibody-related pure red cell aplasia

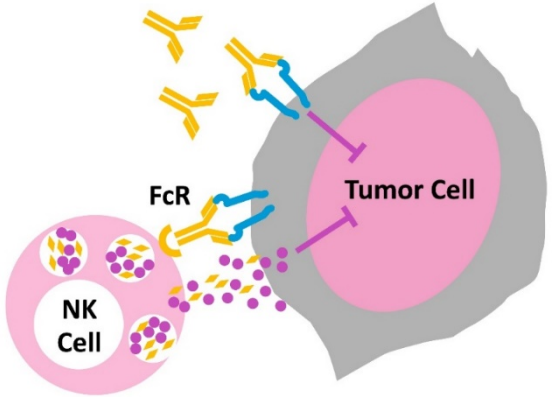
Formulation change

Replacement of albumin by Tween 80/glycine in epoetin alfa (outside USA)



Trastuzumab: αHER2-Monoclonal IgG1 Antibody Postulated Mechanisms of Action[1]

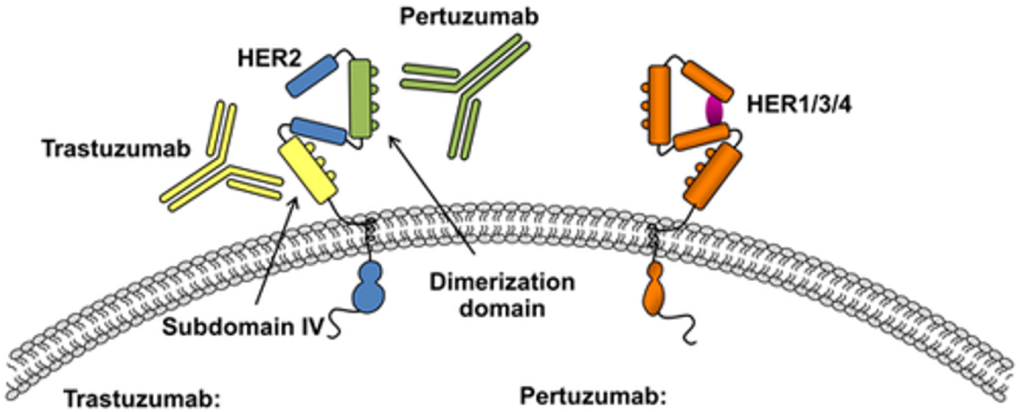
1. Growth Factor Receptor Blockade
Inactivation of AKT signalling
Decreased Cell Proliferation
Induction of Apoptosis



2. $Fc_{\gamma}R$ engagement (e.g. Antibody-Dependent Cellular Cytotoxicity, ADCC)

<u>Preclinical evidence for role of ADCC</u>:
Efficacy of trastuzumab against breast cancer xenografts was largely dependent on FcR binding[2]

Pertuzumab and Trastuzumab:
Study Complementary mechanisms of action

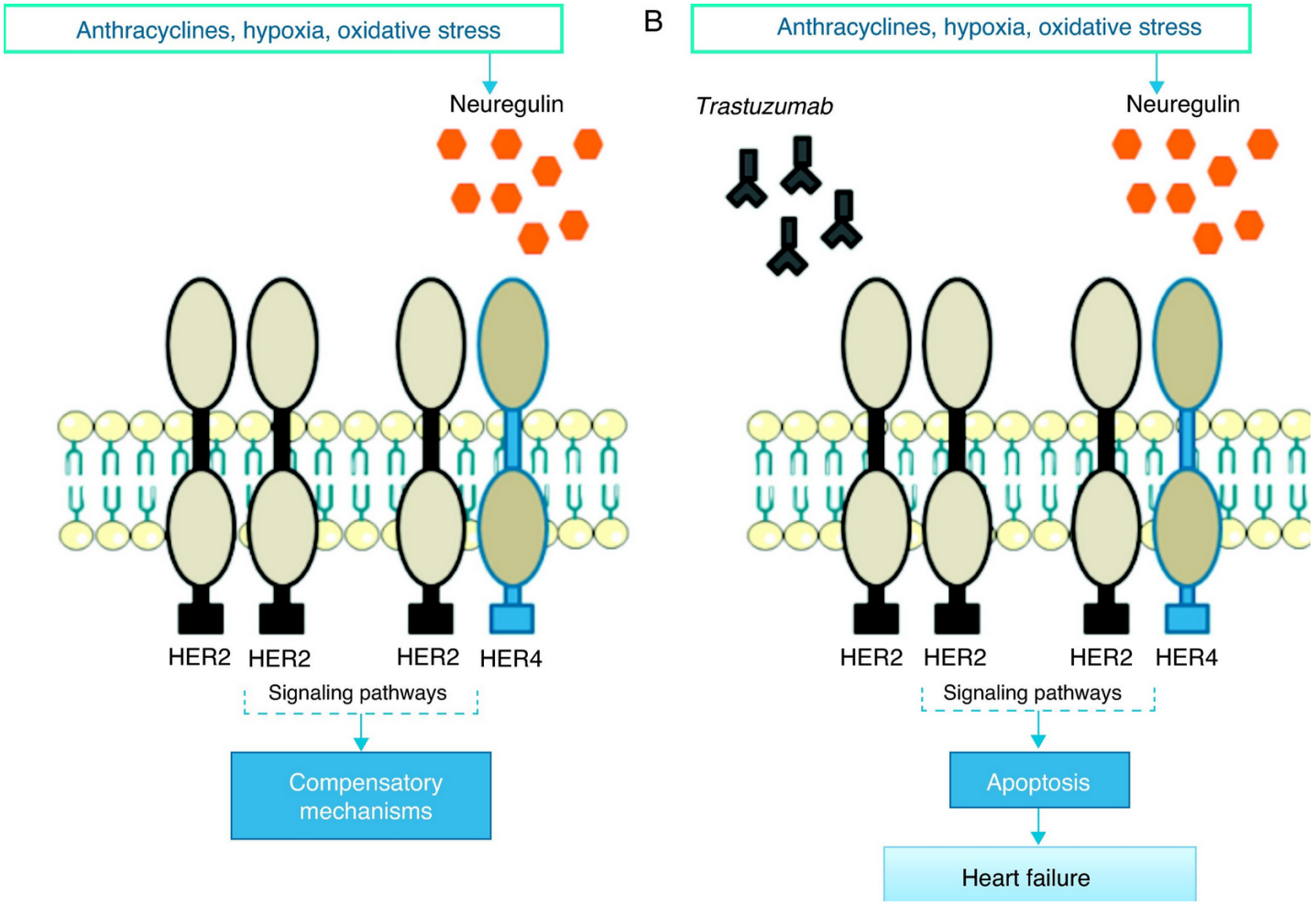


Trastuzumab:
- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

Pertuzumab:
- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

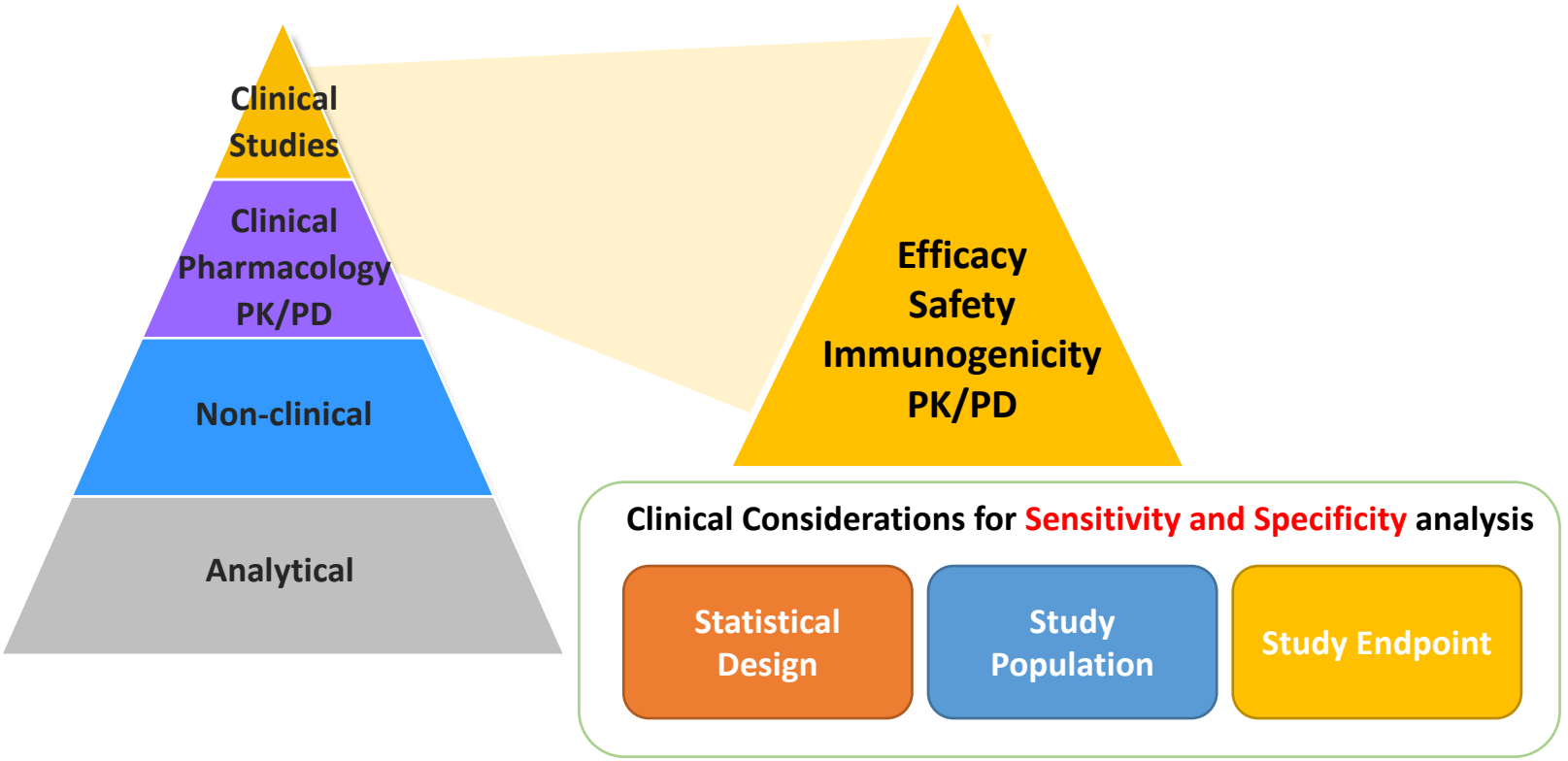
1. Hudis CA. *N Engl J Med* 2007;357:39-51. 2. Clynes RA, *et al. Nature Med* 2000;6:443-446.

Comparative understanding of trastuzumab cardiotoxicity



Clinical Considerations for Establishing Biosimilarity

- Biosimilar development consists of a step-wise comparison to build 'totality of evidence'[1,2]
- Clinical parameters include: Pharmacokinetics (PK), pharmacodynamics (PD), efficacy, safety, and immunogenicity[2]



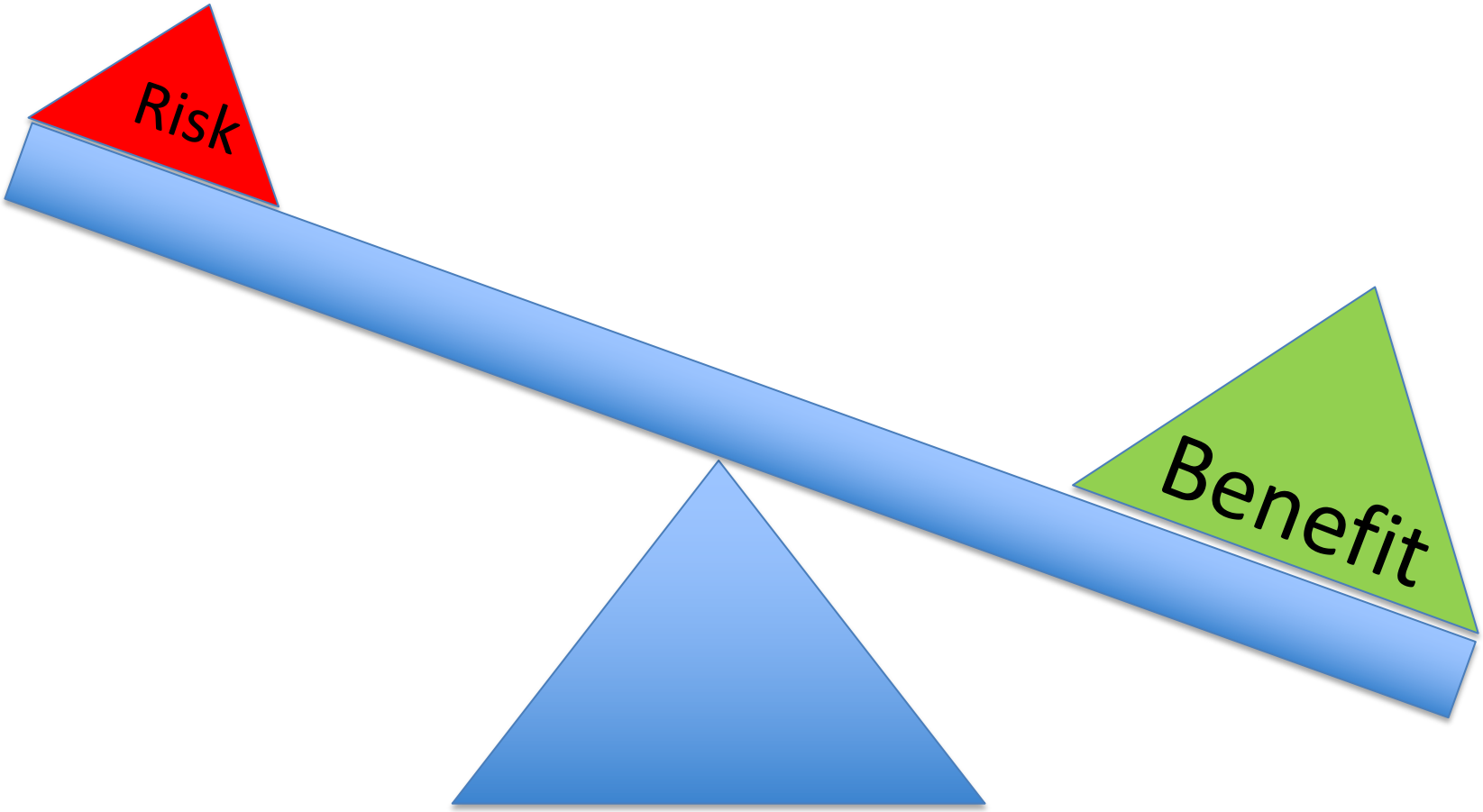
1. EMA Guideline on similar biological medicinal products_2012.
2. FDA Guidance for Industry: Scientific considerations in demonstrating biosimilarity to a reference product_2015 Apr.

Overview of Trastuzumab Biosimilars with Different End-Points and Populations (As of October 2017)

Biosimilar	Patient #	Study Indication	Primary Endpoint	Risk Difference		Risk Ratio	
				Equivalence Margin	Results	Equivalence Margin	Results
ABP-980 Amgen[1]	725	Early	Total pCR	[-13%, 13%]	7.3 % [90%, 1.2%, 13.4%]	[0.759, 1.318]	1.19 [90%, 1.033, 1.366]
CT-P6 Celltrion[2]	562	Early	Total pCR	[-15%, 15%]	-3.62% [95%, -12.38%, 5.16%]	[0.74, 1.35]	0.93 [95%, 0.78, 1.11]
SB3 Samsung Bioepis[3]/MSD	875	Early	Breast pCR	[-13%, 13%]	10.70% [95%, 4.13%, 17.26%]	[0.785, 1.546]	1.259 [90%, 1.112, 1.426]
CT-P6 Celltrion[4]	475	Metastatic	ORR (6 mo)	[-15%, 15%]	-5.4% [95%, -14.3%, 3.6%]	[0.74, 1.35]	0.93 [95%, 0.78, 1.11]
MYL141O Mylan/Biocon[5]	500	Metastatic	ORR (24 wk)	[-15%, 15%]	5.53 [95%, -3.08%, 14.04%]	[0.81, 1.24]	1.09 [90%, 0.974, 1.211]
PF-05280014 Pfizer[6]	690	Metastatic	ORR (25 wk)	N/A	N/A	[0.8, 1.25]	0.94 [95%, 0.842, 1.049]

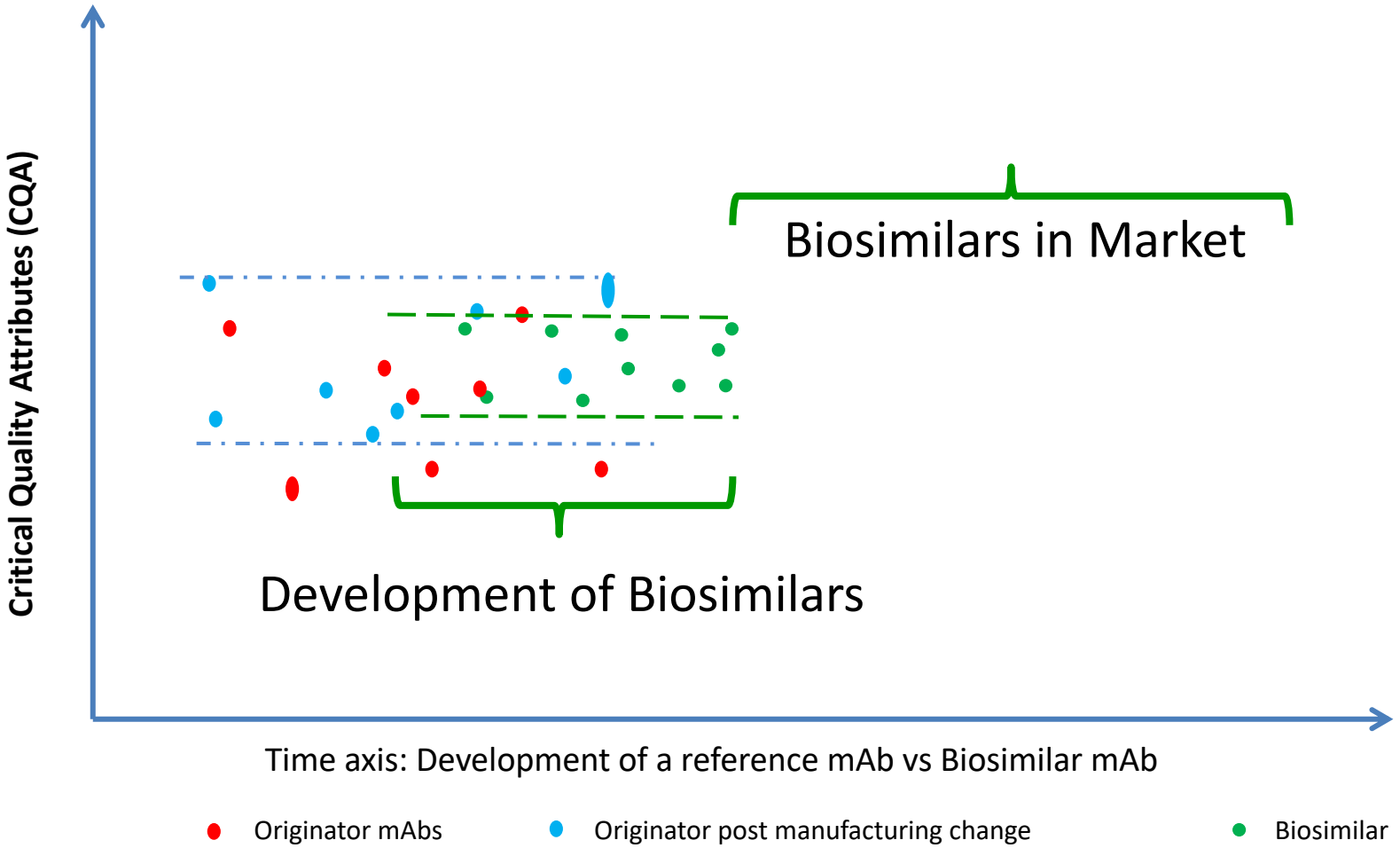
1. von Minckwitz G, *et al.* ESMO 2017, 151PD. 2. Stebbing J, *et al. Lancet Oncol* 2017;18(7):917-928. 3. *J Clin Oncol* 35, 2017 (Suppl; Abstr 509). 4. *J Clin Oncol* 31, 2013 (Suppl; Abstr 629). 5. Rugo HS, et al. *JAMA* 2017;317(1):37-47. 6. Lammers PE, et al. ESMO 2017, 238PD.

Biosimilars: More of a benefit than hazard



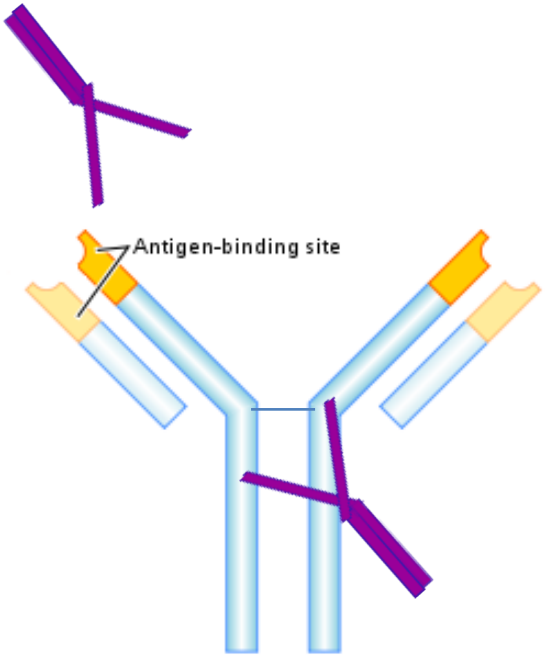
Science and Real-World Evidence

Post-Marketing Assessment and Pharmacovigilance is Crucial to Consolidate Confidence in Biosimilars



Joao Goncalves: Personal communication

A hypothetical cause of concern: Increase in immunogenicity with biosimilars' use?

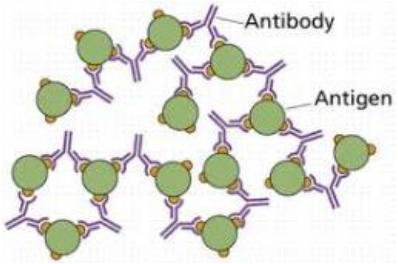


Immune-complex formation:

- Hypersensitivity reactions?
- Alteration in bioavailability?
- No effect?

Clinical efficacy impacted

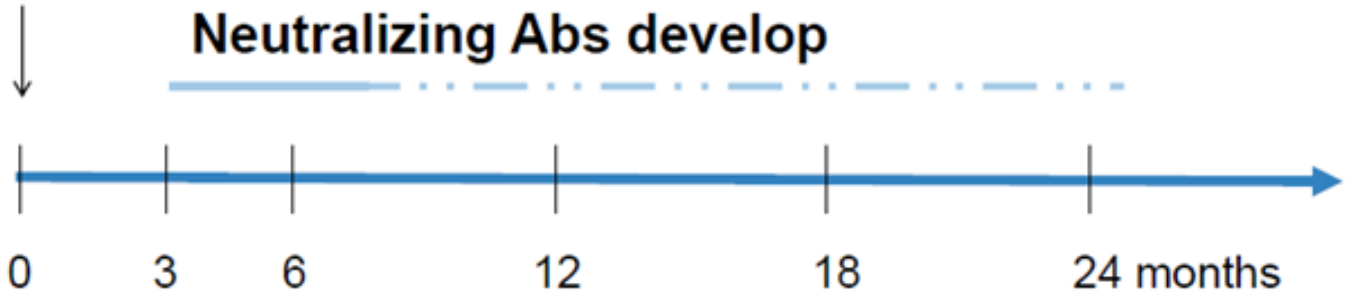
(Infusion reaction)



Trough levels drop

Drug

Neutralizing Abs develop



Goncalves, J et al. Clin Exp Rheumatol. 2016 Jul-Aug;34(4):698-705.

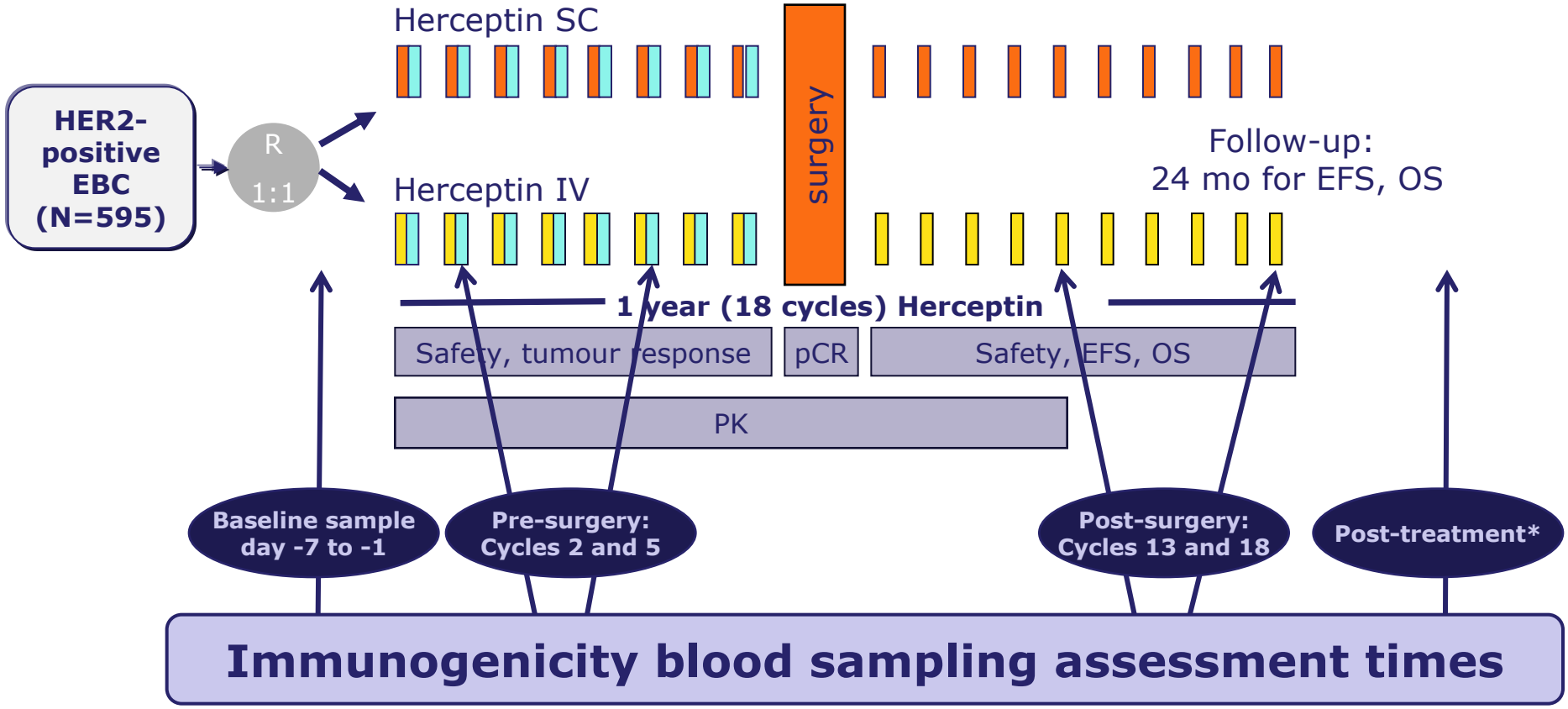
Factors influencing immunogenicity of biologics

Concerning the biosimilar		Not concerning the biosimilar
Associated with product	**Not associated with product**	**Associated with patient**
Self or non-self	Route of administration Risk SC>IV	Haplotype
T cell epitopes	Indication – chronic or acute disease	Tolerance to protein
Formulation/ Impurities/Aggregates	Pharmacokinetics	Immunosuppression
Post-translational modifications	Target – cellular or soluble	Pathology

IV, intravenous; SC, subcutaneous.

Pradeu T, et al. Nat Rev Immunol 2013;13:764–9; Schaeverbeke T, et al. Rheumatology (Oxford) 2016;55(2):210–20.

Herceptin subcutaneous development programme in the most sensitive population



*Anti-drug antibody samples collected at follow-up visits at 3, 6, 12, 18 and 24 months

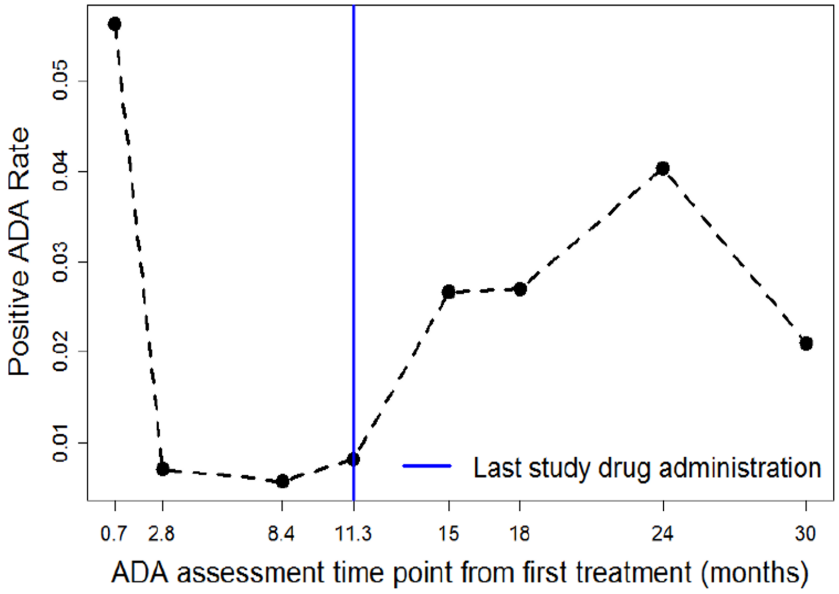
Herceptin SC
Fixed dose of 600 mg

Herceptin IV
8 mg/kg loading dose;
6 mg/kg maintenance dose

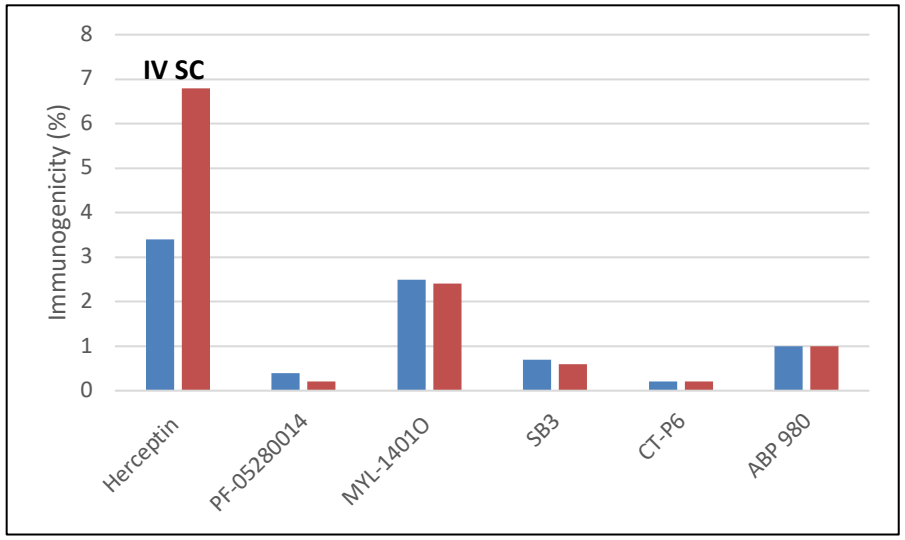
Chemotherapy
(T x 4→FEC x 4)

Immunogenicity detection is increased in a setting with a treatment-free follow-up

Hanna Study: Immunogenicity between SC and IV Trastuzumab



Overview of Trastuzumab immunogenicity (Original and Biosimilars)



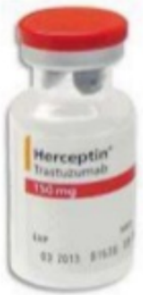
Stability and quality of biologic drugs end at manufacturing site?

Handling and Storage of Biologicals

Degradation of mAb's

How many types of degradation do we contribute to when preparing a product?

Lyophilized powder



Reconstituted vial

Infusion bag

Degradation of mAbs

How many types of degradation do we contribute to when preparing a product?

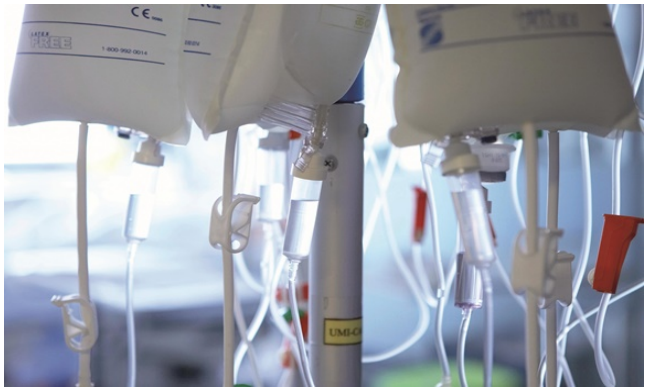
Removing from the fridge

Adding diluent

Reconstituting

Introducing to infusion bag

But no published Comparative Stability Drug data in Real-Life Hospital Pharmacy for original biologics and biosimilars!!



Surface interactions (Containers)

- **Adsorption** - interact with all types of surfaces. Can potentially interact with devices during production and storage
- **Leaching** – presence of solubilising agents in the formulation increases likelihood of leaching.
- **Silicon** – act as nucleation sites in certain circumstances

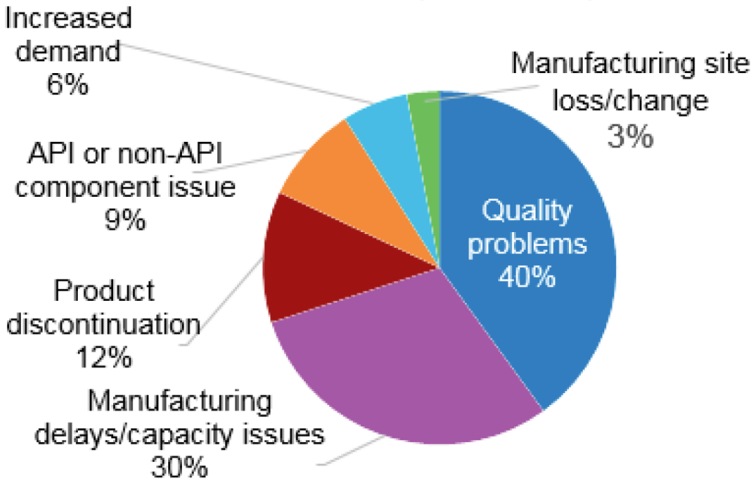
mAbs have different stabilities

Attribute	Method	Trastuzumab	Rituximab	Infliximab	Cetuximab
Visible particles	Visual inspection	+	-	+	-
Turbidity	Visual inspection	++	-	++	+
µm-particles	MFI	++	+	++	+
nm-particles	NTA	-	++	++	++
HMW species	SEC	-	-	-	+
Protein recovery	SEC	+	-	+	-
LMW species	SEC	-	+	+	-
Conformational instability	nDSF	-	-	-	-
Charge variants	cIEF	-	-	-	-

- = not affected (relative to control)
+ = affected (relative to control)
++ = highly and/or immediately affected

Drugs for oncology are frequently affected by shortages

Reported causes of drug shortages in the US (2011–2013)[1]



Immediate cause of drug shortages is often a manufacturer halting or slowing production to address quality problems[1]

Shortage or lack of batches' consistency affect stability?

"Given that CT-P13 has been developed as a biosimilar medicinal product, stability testing has also been performed using Remicade. Specifically, batches of Remicade have been assessed following storage at various conditions (……). The protein content for the tested Remicade batches fell below the proposed commercial CT-P13 end-of-shelf-life specification at the 12 months testing time point; this was attributed to the fact that the Remicade batches in the stability study were 'older' than the CT-P13 batches at the time the study was initiated. For accelerated and stress stability testing, it was demonstrated that CT-P13 and Remicade have a comparable degradation profile.

EMA, 2014 (EPAR Inflectra/Remsima)

We need well documented long-term stability data for biologics in the **Hospital Pharmacy**

- It is critical to have well-documented data about the stability of an opened drug formulation, after reconstitution of a lyophilized product or after dilution in various vehicles.
- Study the effects of IV infusion procedure on aggregates and particles between original biologic and biosimilars.
- Quantify and characterize particles, aggregates and leachates between original biologic and biosimilars in real-life hospital.
- Data of stability as a function of time during run, saline bag type, filter size/brand, location in IV system, etc.

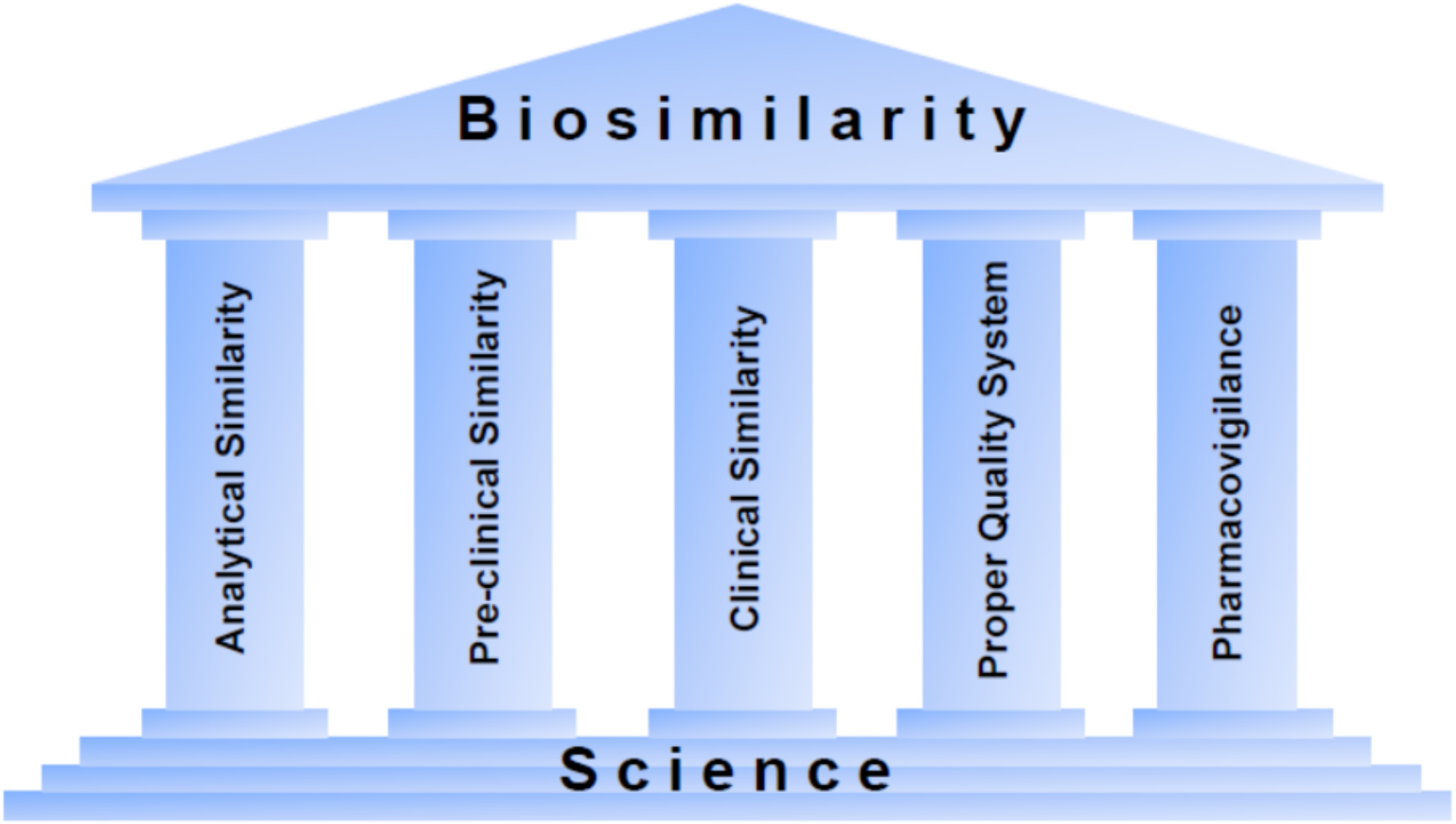
Goal is to understand effects & optimize proper handling to minimize aggregation/particle formation during IV administration between original antibodies and biosimilars.

Real-life data for biologics and biosimilars in the Hospital Pharmacy

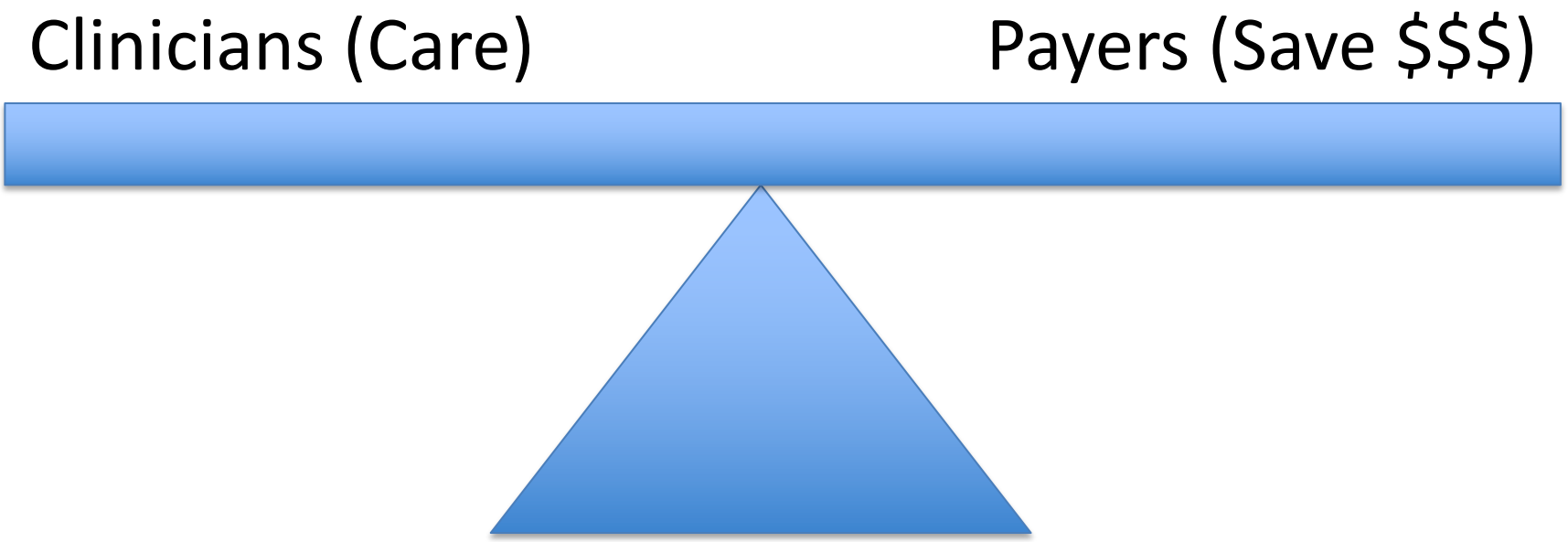
Important: Correlation with clinical data

- Immunogenicity and PK is not only useful for clinical decision
- It should be used by the hospital pharmacy in aggregated form to control the quality of the drug and how the patients react to the original biologic and biosimilar.
- The immunogenicity and PK data of the patient population is a key factor to validate the use of biosimilars.
- Highly important in active pharmacovigilance.

Conclusion…


Biosimilarity
Analytical Similarity
Pre-clinical Similarity
Clinical Similarity
Proper Quality System
Pharmacovigilance
Science

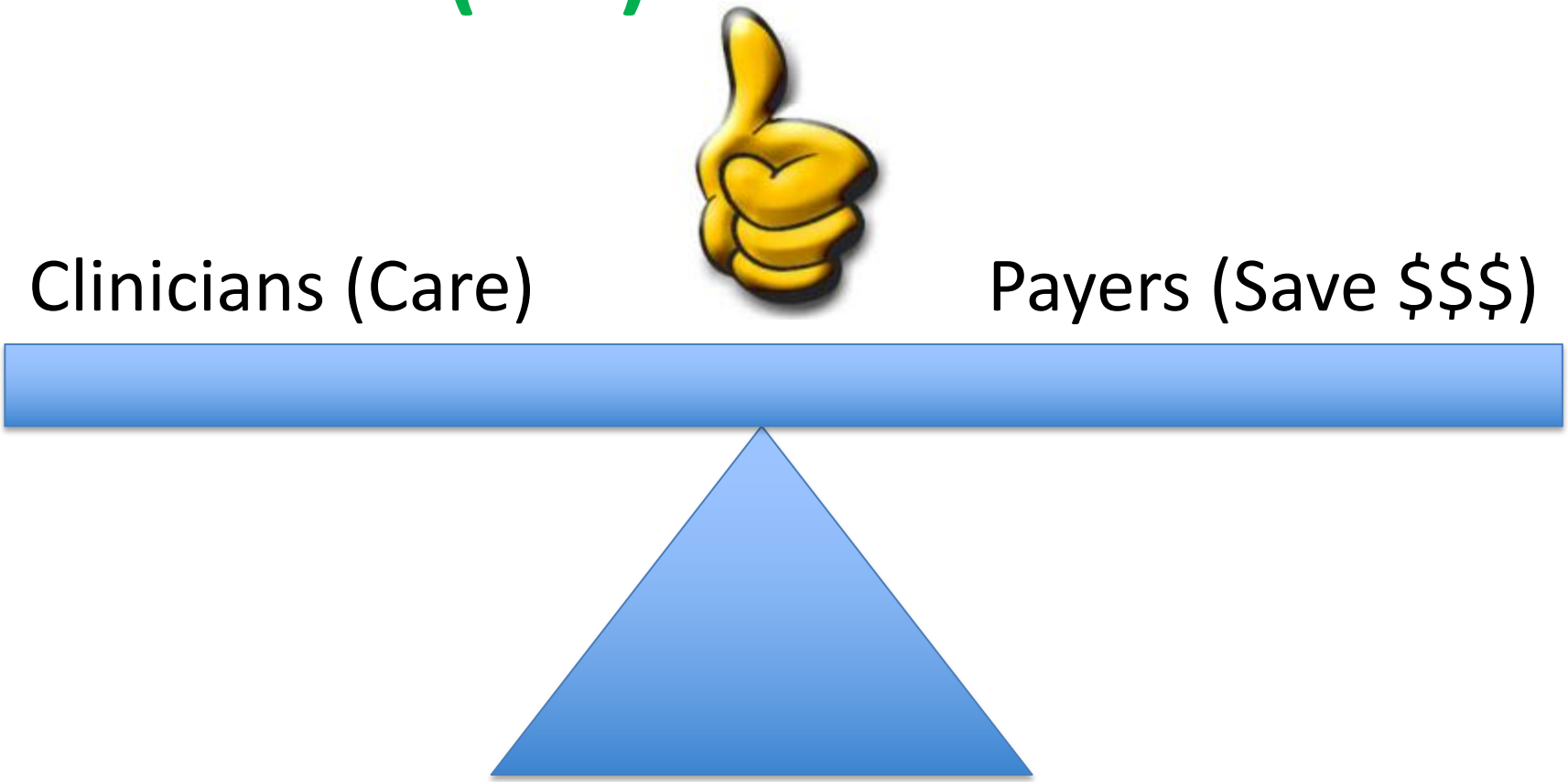
Patient Access to better treatments



Hospital Pharmacists

Guardians of drug quality and access

Patient Access to better (Bio) treatments



Hospital Pharmacists

Guardians of drug quality and access

Thank You/Obrigado

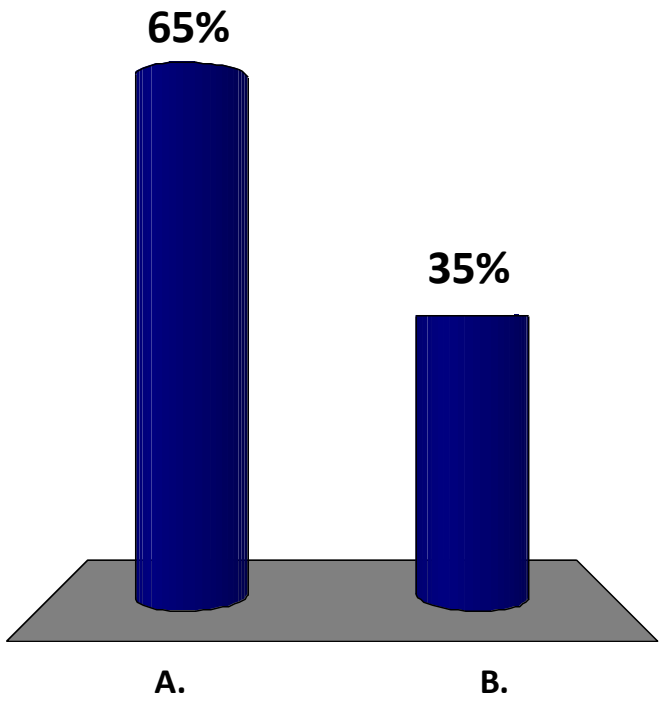
joao.goncalves@ff.ul.pt

Lisbon - Not a biosimilar of San Franscisco

Protein aggregation is the most importante critical quality atribute of a biosimilar trastuzumab that implicates diferences in efficacy.

✓ A. True

B. False



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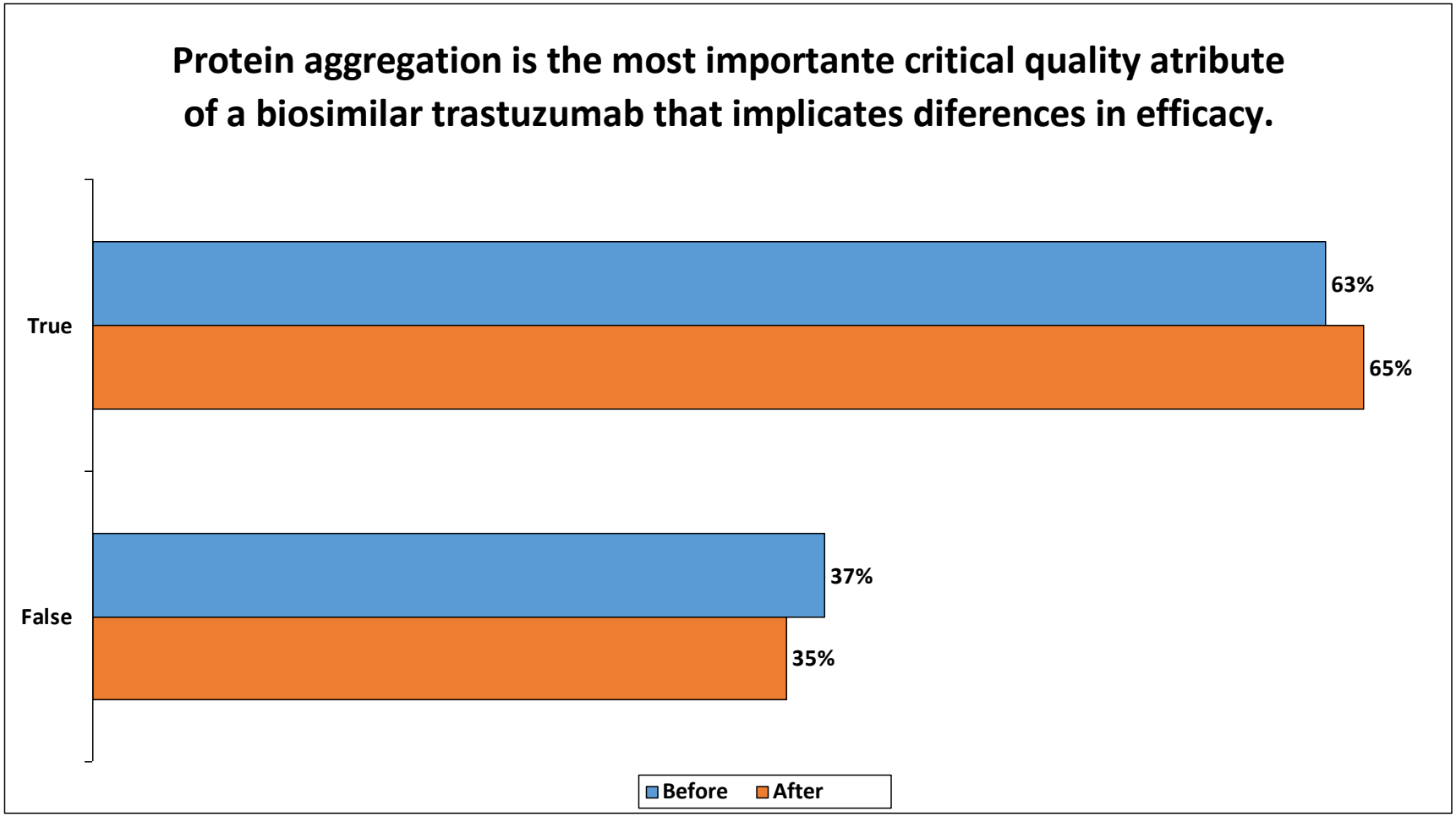
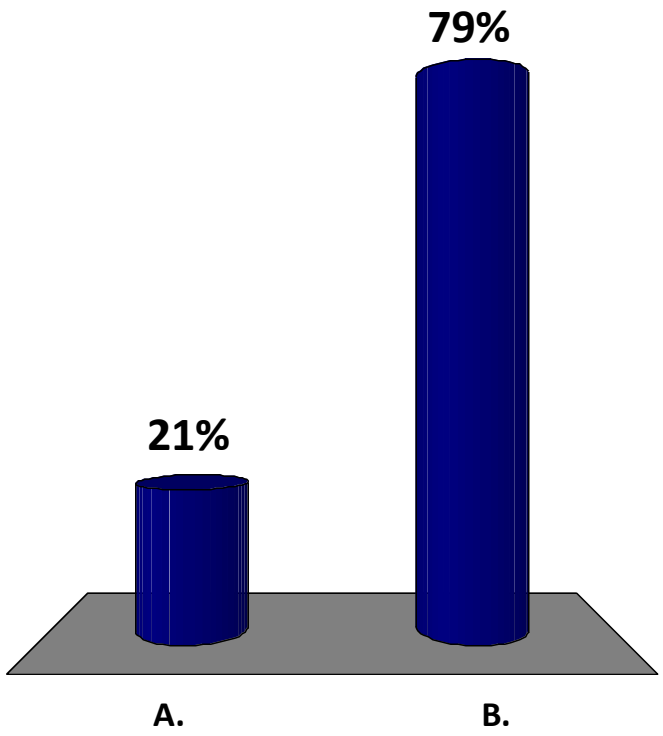
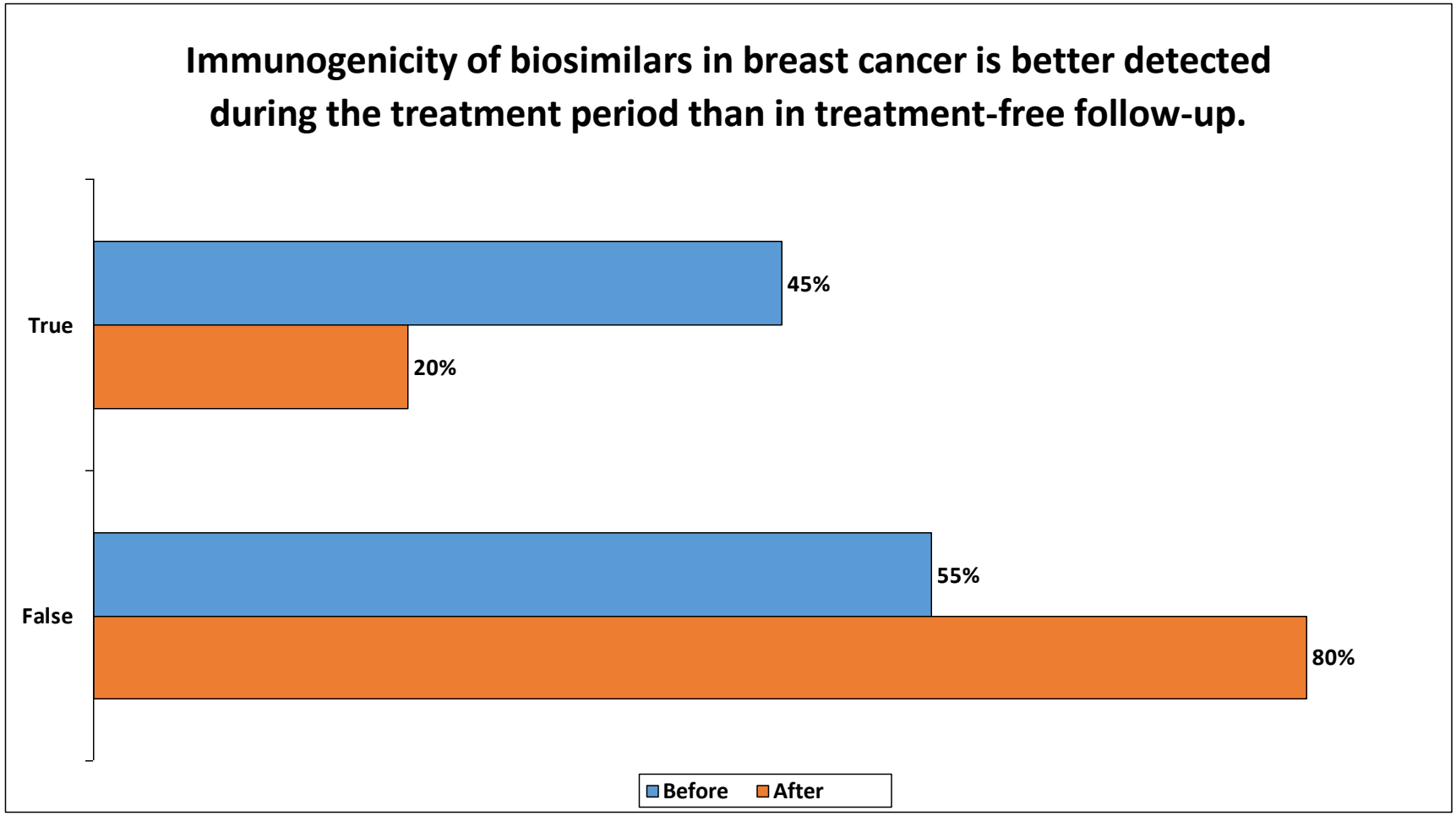


Immunogenicity of biosimilars in breast cancer is better detected during the treatment period than in treatment-free follow-up.

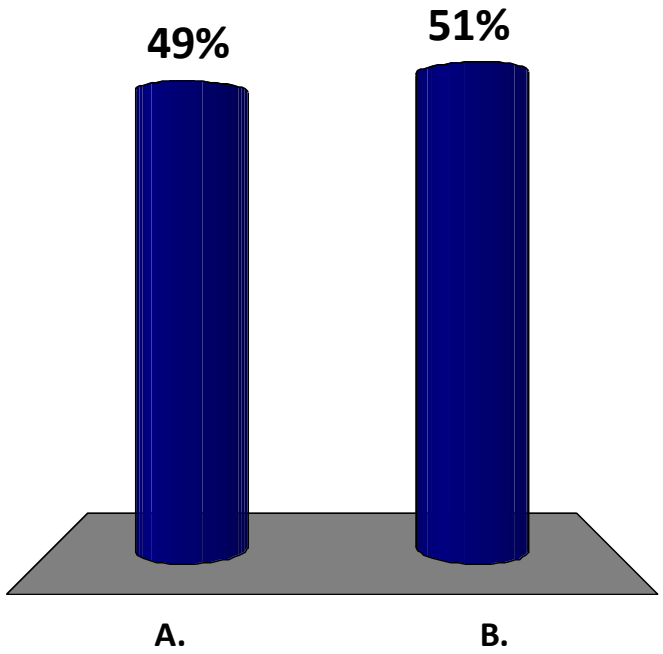
A. True
✓ B. False




Immunogenicity of biosimilars in breast cancer is better detected during the treatment period than in treatment-free follow-up.
True
False
45%
20%
55%
80%
Before
After

Batch to batch variability, and consequently increase risks for phramacovigilance, is inherent to biosimilars and should be taken with precaution.

A. True
✓ B. False



Batch to batch variability, and consequently increase risks for phramacovigilance, is inherent to biosimilars and should be taken with precaution.