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CONGRESS – PUTTING PATIENT FIRST
22 NOVEMBER 2014

Regulating the development and approval of biosimilar monoclonal antibodies – Considerations on some Regulatory and Clinical Topics

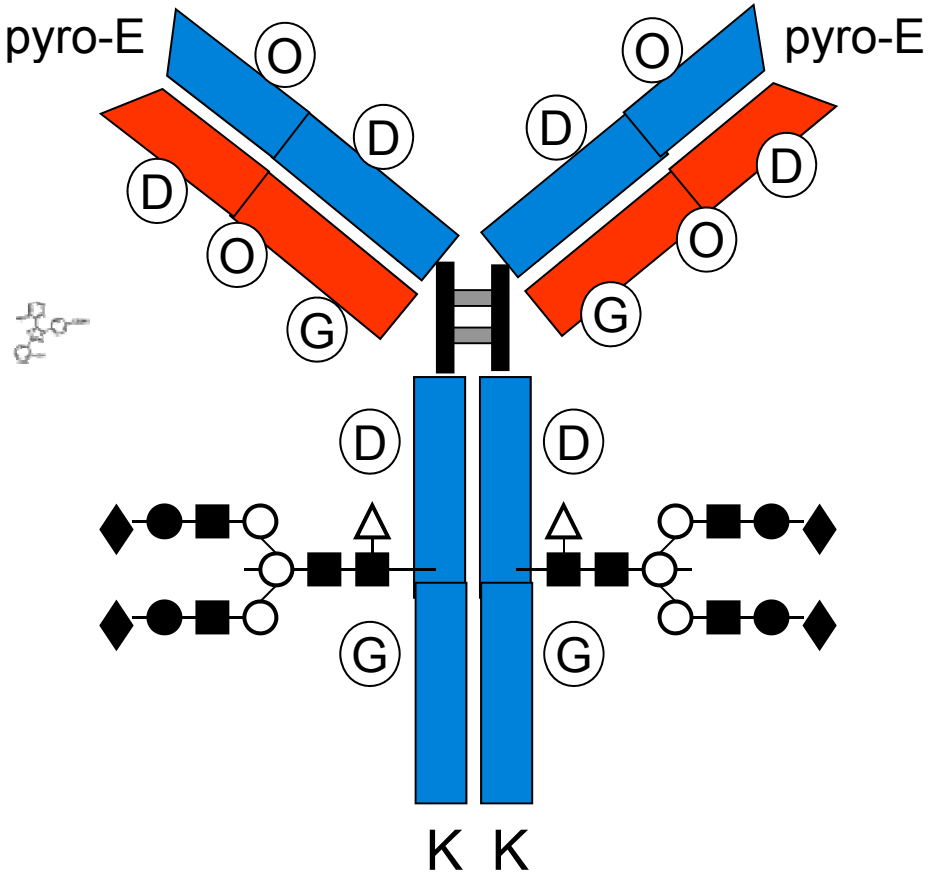
Dr. Thomas Schreitmueller, Regulatory Policy, Biologics

PhAMA

1ST NATIONAL BIO-THERAPEUTICS

Biological product complexity:

Examples of modifications: inherent or due to the manufacturing process

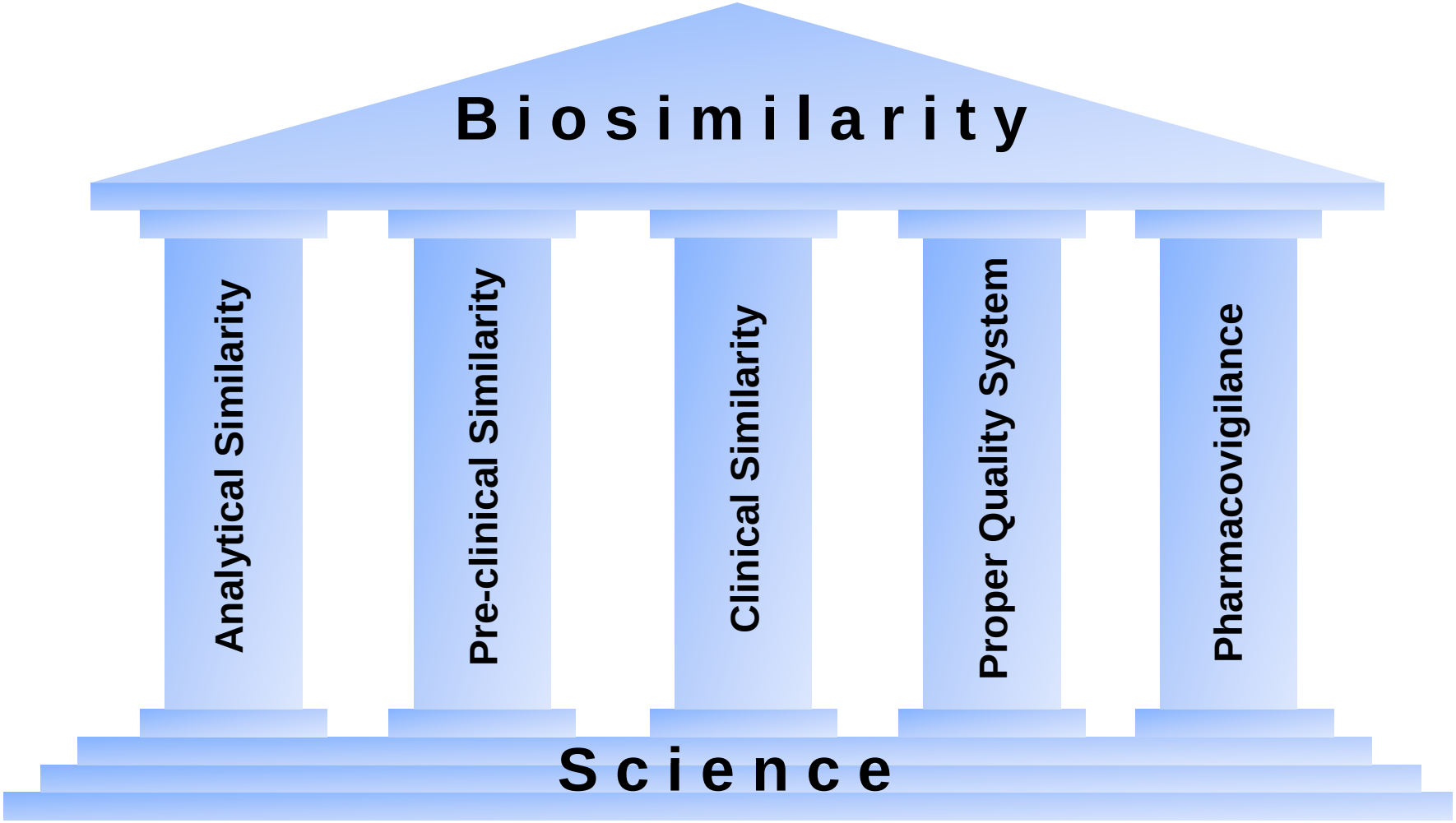


- Pyroglutamyl peptides
- Deamidation
- Methionine oxidation
- Glycation
- High mannose, G0, G1, G1, G2
- Sialylation
- C-terminal Lysine

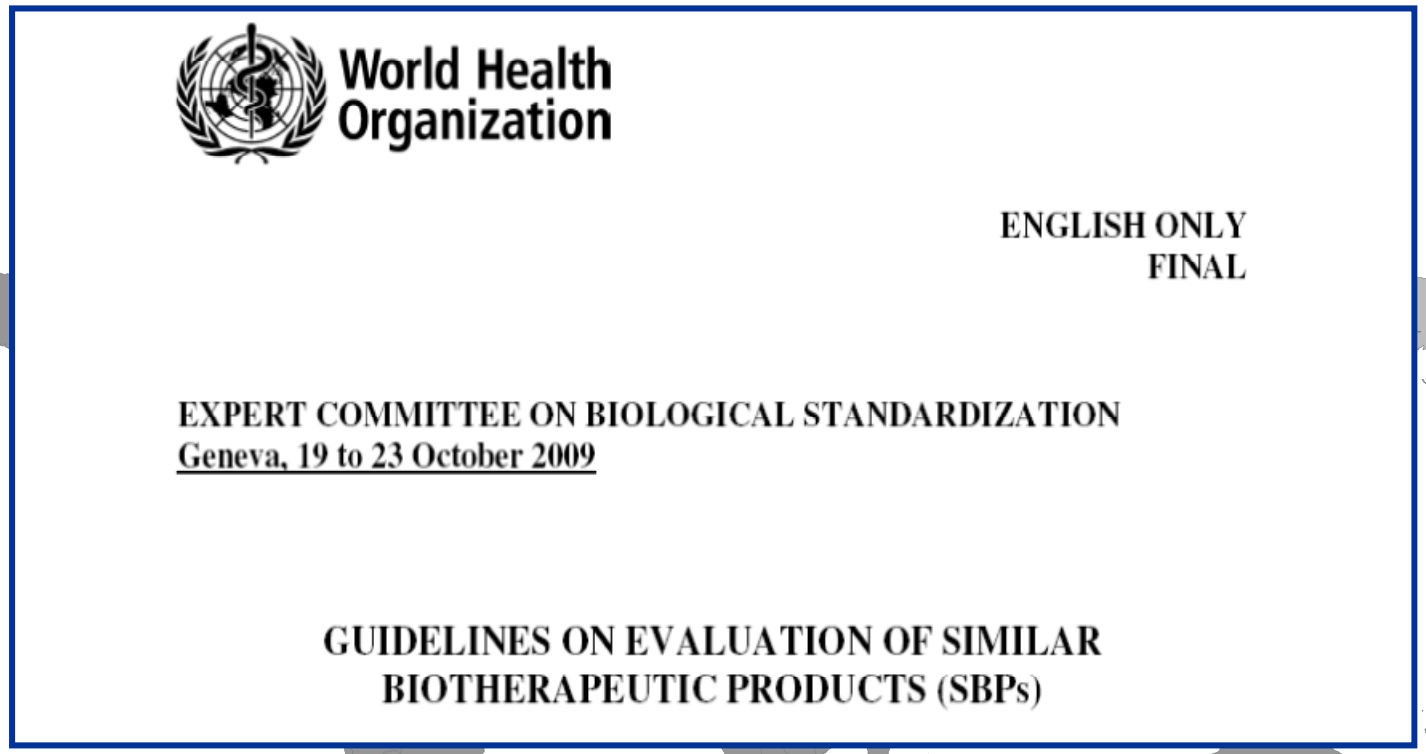
Modifications may result in approximately 10^8 potential variants

Adapted from: *Steven Kozlowski; FDA*

Based on science, the Concept of Biosimilarity globally agreed is built on five indispensible pillars:



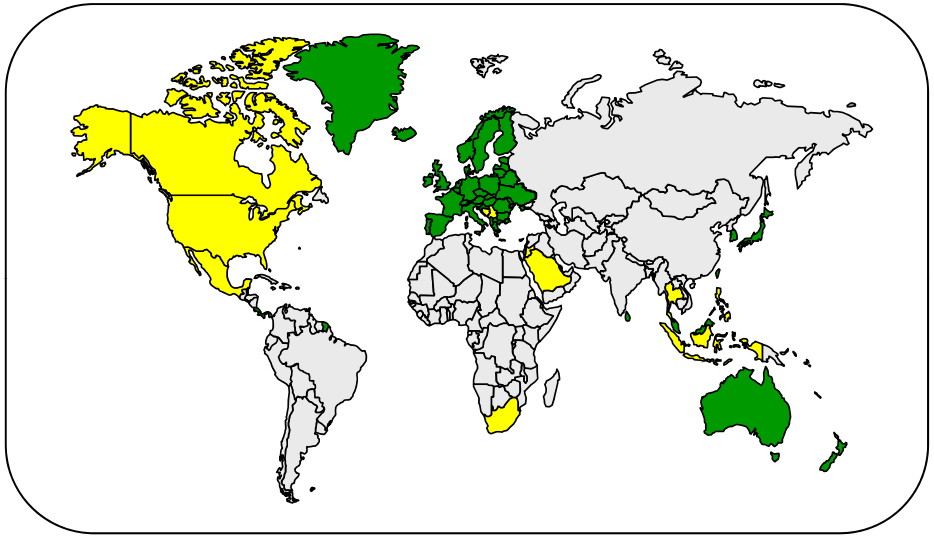
The WHO Guidance for biosimilars



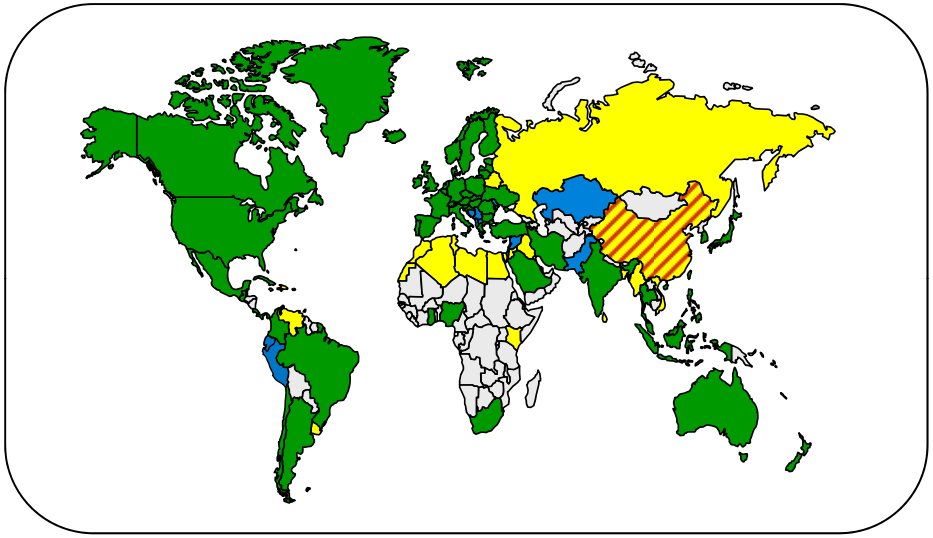
WHO global guideline published April 2010

Global Progress on the Developments of Regulatory Framework for Biosimilars

Before 2010



Sept. 2014



- Biosimilar pathways
- Law in place
- Biosimilar pathways under development

Outcomes of WHO survey in 2014 (1)

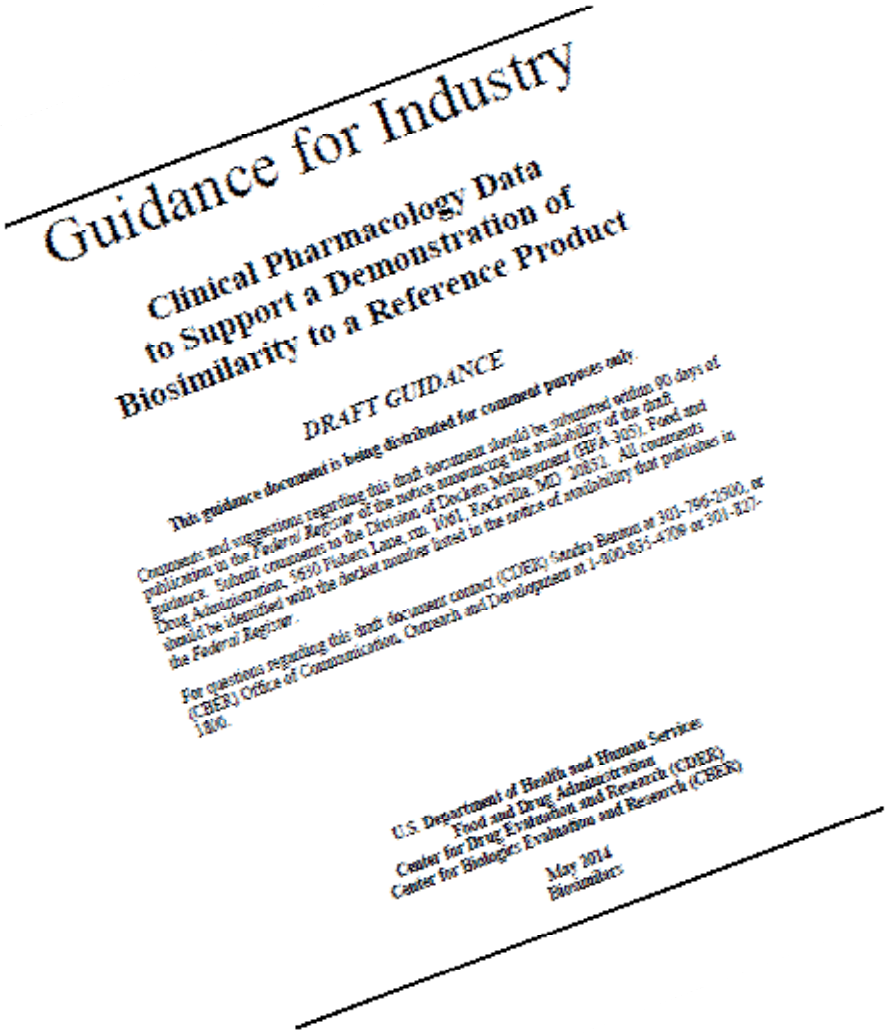
- **Q 1. Countries where SBP regulation is …**
  - …in place: Brazil, Canada, Ghana, India, Iran, Japan, Jordan, Korea, Malaysia, Peru, Philippines, Singapore, Thailand, EU
  - …under development: Burkina Faso, China, Egypt, Indonesia (since 2010 implementing WHO Guidelines), Tanzania, Zambia

- **Q 2. Licensed SBPs – global picture as of April 2014**
  - Same SBPs as in EU are also licensed in other 46 countries
  - SBP not licensed in EU: Jordan, Indonesia, Japan, Korea, Malaysia
  - Unclear evaluation: Ghana, Tanzania, Zambia, Iran
  - No SBP: Burkina Faso, India, Thailand, Egypt, Philippines, Peru, China, Cuba

Experience to date: authorized biosimilars in the EU

	Product and Brand	Company	Extrapolation
1	Omnitrope (somatropin)	Sandoz	Full Label
2	Valtropin (somatropin)	Biopartners	Full Label
3	Binocrit (epo alfa)	Sandoz	Full label - I.V.
4	Epoetin alfa Hexal (epo alfa)	Hexal	Full label - I.V.
5	Abseamed (epo alfa)	Medice	Full label - I.V.
6	Silapo (epo zeta)	Stada	Full label - I.V.
7	Retacrit (epo zeta)	Hospira	Full label
8	Filgrastim Ratiopharm (filgrastim)	Ratiopharm	Full Label
9	Ratiograstim (filgrastim)	Ratiopharm	Full Label
10	Biograstim (filgrastim)	CT Arzneimittel GmbH	Full Label
11	Tevagrastim (filgrastim)	Teva	Full Label
12	Filgrastim Hexal (filgrastim)	Hexal	Full Label
13	Zarzio (filgrastim)	Sandoz	Full Label
14	Nivestim (filgrastim)	Hospira	Full Label
15	Remsima (infliximab)	Celltrion	Full Label
16	Inflectra (infliximab)	Hospira	Full Label
16	Ovaleap (follitropin alfa)	Teva	Full Label
17	Abasria (insulin glargine)	BI/Lilly	tbd

New FDA Biosimilar Guidance



Guidance for Industry

Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Sandra Benson at 301-796-2500, or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2014
Biosimilars

Results of analytical characterization inform the next steps in the demonstration of biosimilarity

- **Not similar:**
  - **further development through the 351(k) regulatory pathway is not recommended**
  - unless, for example, **modifications are made to the manufacturing process** for the proposed biosimilar product that is likely to lead to a highly similar biological product.

- **Similar:**
  - **Additional analytical data or other studies are necessary** to determine if observed differences are within an acceptable range to consider the proposed biosimilar product to be highly similar to the reference
  - E.g. **comparative PK and PD studies of the proposed biosimilar product and the reference product help resolve that some differences in e.g. glycosylation** identified in the analytical studies would be within an acceptable range to consider the proposed biosimilar product to be highly similar to the reference product.

US FDA Guidance for Industry, Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

Results of analytical characterization inform the next steps in the demonstration of biosimilarity

- **Highly similar:**
  - The proposed biosimilar product meets the statutory standard for analytical similarity.
  - The results of the comparative analytical characterization permit **high confidence in the analytical similarity** of the proposed biosimilar and the reference product
  - It is ppropriate for the sponsor to **conduct targeted and selective animal and/or clinical studies** to resolve residual uncertainty and support a demonstration of biosimilarity.
- **Highly similar with fingerprint-like similarity:**
  - The Product meets the statutory standard for analytical similarity based on **integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences**
  - **Permits a more targeted and selective approach to conducting animal and/or clinical studies** to resolve residual uncertainty and support a demonstration of biosimilarity.

US FDA Guidance for Industry, Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

Case study: approval of the first monoclonal antibody in Europe

- **Infliximab** (Remsima / Inflectra)
  - Anti-TNFα antibody
    - Chimeric human-murine IgG monoclonal Ab
    - Binds to TNFα and neutrolizes TNFα activity

- **Reference Medicinal Product Remicade**
  - Indications: Rheumatoid Arthritis (infliximab + methotrexate), adult & paediatric Crohn's disease, ulcerative colitis (adult & paediatric), ankylosing spondylitis, psoriatic arthritis, psoriasis.

Adapted from Anne Cook, EUCRAF 2014

TNF – tumour necrosis factor

Infliximab Mechanism of Action

- “It is currently believed that neutralisation of sTNF and tmTNF is responsible for its efficacy in RA by preventing TNF from inducing TNFR-mediated cellular functions”.
- “It can also be accepted that the effects of infliximab blockade on synovial inflammation are comparable in different forms of arthritis. Such effects are also believed to play a role in psoriasis plaques”.
- “However, more mechanisms are likely involved in inflammatory bowel diseases (IBD), which are related to its binding to tmTNFα and include reverse signalling and Fc-related effector functions. The relative contribution of these various effects is currently unknown”.

EMA. Remsima: EPAR – Product Informatio

EMA EPAR: Product Quality

- The CHMP noted “a small difference in the amount of afucosylated infliximab, translating into a lower binding affinity towards specific Fc receptors and a lower *ex vivo* antibody-dependent cellular cytotoxicity (ADCC) activity in the most sensitive ADCC assay. “
- “Celltrion argued that this difference was not considered clinically meaningful, as it did not affect the activities of Remsima in experimental models regarded as more relevant to the pathophysiological conditions in patients “

    --in blood (serum of Crohn’s disease patient),

    --inflammatory setting: LPS-stimulated monocytes as target cells/PBMC as effector cells

    --in a wound healing model using induced cells that include these macrophages on a culture of human colorectal epithelium cells.

EMA. Assessment report: Remsima (EMA/CHMP/589317/2013). June 27 20

The consequences of being similar but not highly similar: Infliximab approvals

	Indications	Molecular Effect of Infliximab Therapy
Approved by Health Canada for Remsima	Rheumatoid Arthritis	Reduced infiltration of inflammatory cells into inflamed areas of the joint as well as reduced expression of molecules mediating cellular adhesion, chemoattraction, and tissue degradation.
	Ankylosing Spondylitis	Reduced serum IL-6 and VEGF and increased serum levels of markers of bone formation (bone alkaline phosphatase and osteocalcin).
	Psoriatic Arthritis	Reduced number of T cells and blood vessels in the synovium and psoriatic skin lesions as well as a reduction of macrophages in the synovium.
	Plaque Psoriasis	Reduced epidermal thickness and infiltration of inflammatory cells, downregulated percentage of activated and cutaneous lymphocyte antigen (CLA)-positive inflammatory cells, and upregulated percentage of CD1a-positive epidermal Langerhans cells.
Not Approved by Health Canada for Remsima	Crohn's Disease	Reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduced proportion of mononuclear cells in the lamina propria able to express TNFα and interferon-γ *(ex vivo).*
	Pediatric Crohn's Disease	*Same as above*
	Ulcerative Colitis	decreased serum levels of the proinflammatory molecules with statistically significant and consistent decreases observed for IL-2R, and ICAM-1
	Pediatric Ulcerative Colitis	*Same as above*

* Indicates actual clinical data generated for submission

Celltrion Healthcare Co. Ltd. REMSIMA Product Monograph. Jan 15 20
Janssen Inc. REMICADE Product Monograph. Aug 26 2013

Health Canada: Summary Basis of Decision for Remsima Approval

- Celltrion did not receive extrapolation to IBD and Crohn's because:
  - Observed **differences in afucosylation** species of **Remicade/Inflectra as compared to Remicade**
  - The potential impact that **this difference** has on the FcγaIIIa receptor and **induction of ADCC; ADCC could not be ruled out**
  - Cell-based **assays were not conclusive**/difficult to exclude ADCC activity
  - **Pathophysiological differences** exist **between RA and the IBDs**
  - **Safety profile differences**, in particular hepatosplenic T-cell lymphoma, is uniquely associated **with inflammatory bowel diseases**

30 May 2012
EMA/CHMP/BMWP/403543/2010
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues

Draft Agreed by Similar Biological Medicinal Products Working Party	**October 2010**
Adoption by CHMP for release for consultation	18 November 2010
End of consultation (deadline for comments)	31 May 2011
Final agreed by BMWP	March 2012
Adoption by CHMP	30 May 2012
Date for coming into effect	1 December 2012

Keywords	***Biosimilars, monoclonal antibodies, similar biological medicinal products, relevant animal model, non-clinical studies, in vitro studies, clinical use, clinical endpoints, extrapolation***

Biosimilar pathways – EMA biosimilar antibody guideline

- The guideline is setting the stage for the overall stepwise development approach having the goal **"…ensuring that the previously proven safety and efficacy of the drug is conserved."**.
- The stepwise approach at the clinical side is outlined more clearly focusing on the main principles to be considered when establishing clinical similarity: **"The guiding principle is to demonstrate similar clinical efficacy and safety compared to the reference medicinal product, not patient benefit per se**, which has already been shown for the reference medicinal product.".
- This has to be achieved by planning **all studies "…with the intention to detect any potential differences between biosimilar and reference medicinal product and to determine the relevance of such differences, should they occur.".**

Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies. Non-clinical and Clinical Issues. EMA/CHMP/BMWP/403543/2010

What is a sensitive and homogeneous population and endpoints?

- The idea is to study the biosimilar in the population of patients in whom – *if there is a difference between biosimilar and reference product* – that difference will most easily be detected
  - **for example, we have a treatment that works in 60% of patients.** If we were able to identify who are the "responder" patients, then we would target treating just those patients
- **Activity endpoints with a large effect size may be considered** as PFS, DFS and OS may not be suitable
  - CR, ORR (also measured at a certain timepoint), percentage change in tumour mass from baseline, or pathological Complete Response (pCR) in certain clinical settings

Frank A Scappaticci,[1] Hans Ulrich Burger,[2] Fabio Bisordi,[2] Fermin Ruiz de Erenchun,[2] Thomas Schreitmüller[2]

[1]Genentech, San Francisco, CA, USA; [2]F. Hoffmann-La Roche Ltd, Basel, Switzerland

Background:

Trastuzumab (Herceptin®) is approved for HER2-positive EBC, MBC

Trastuzumab biosimilars raise questions about conducting mandat

clinical equivalence studies, to show similarity in efficacy, safety

and mitigate risks associated with extrapolation to indications n

biosimilar mAb. EMA mAb biosimilar guidelines recommend s

homogenous populations and sensitive endpoints for such s

populations are generally heterogenous, and pts may hav

response. Establishing clinical similarity in the neoadjuva

the better risk mitigation strategy for extrapolating clinic

more acceptable to regulators than the reverse.

RESEARCH ARTICLE

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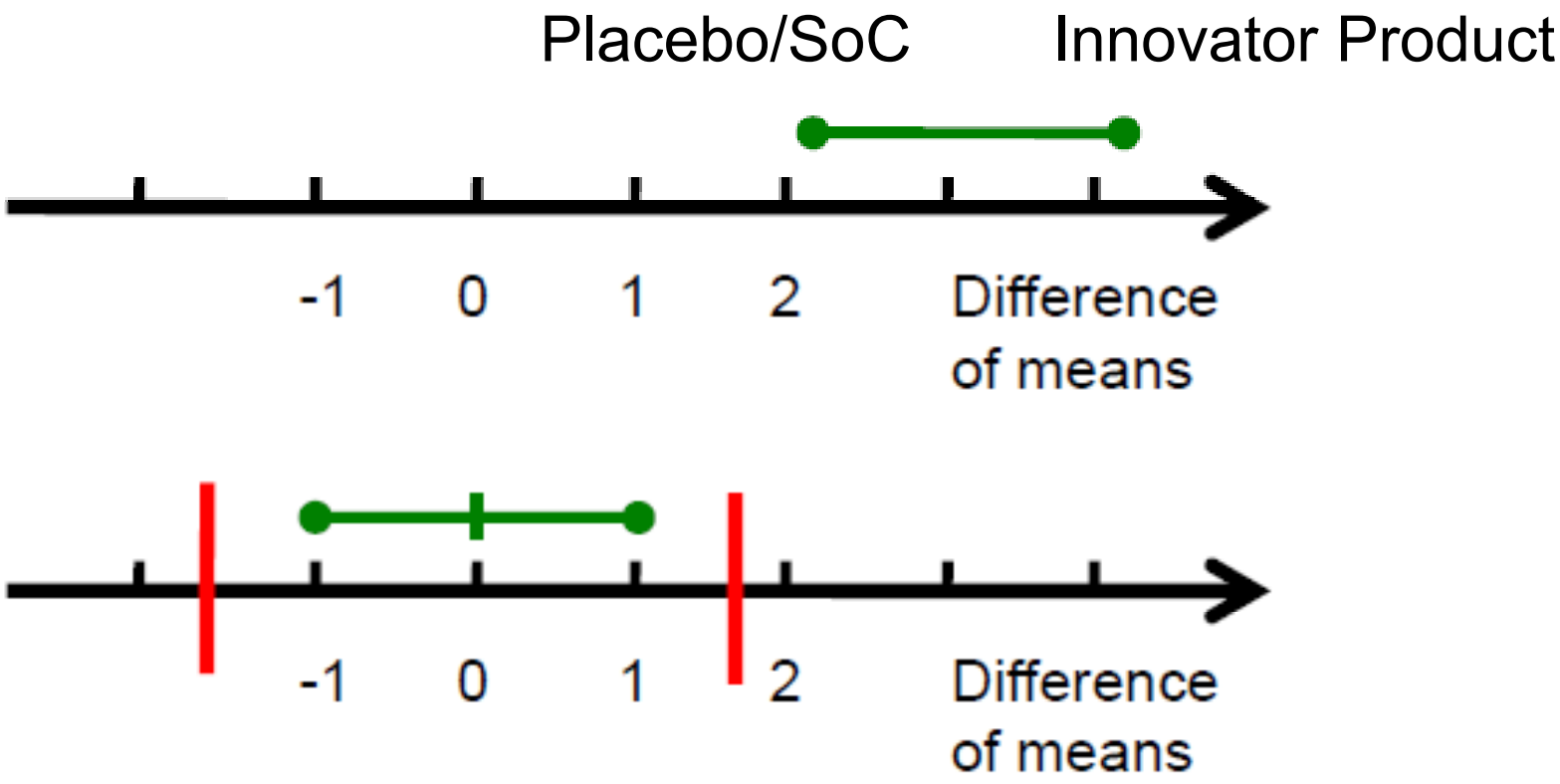
Future ONCOLOGY

Neoadjuvant breast cancer treatment as a sensitive setting for trastuzumab biosimilar development and extrapolation

Christian Jackisch*[1], Frank A Scappaticci[2], Dominik Heinzmann[3], Fabio Bisordi[3], Thomas Schreitmüller[3], Gunter von Minckwitz[4] & Javier Cortés[5]

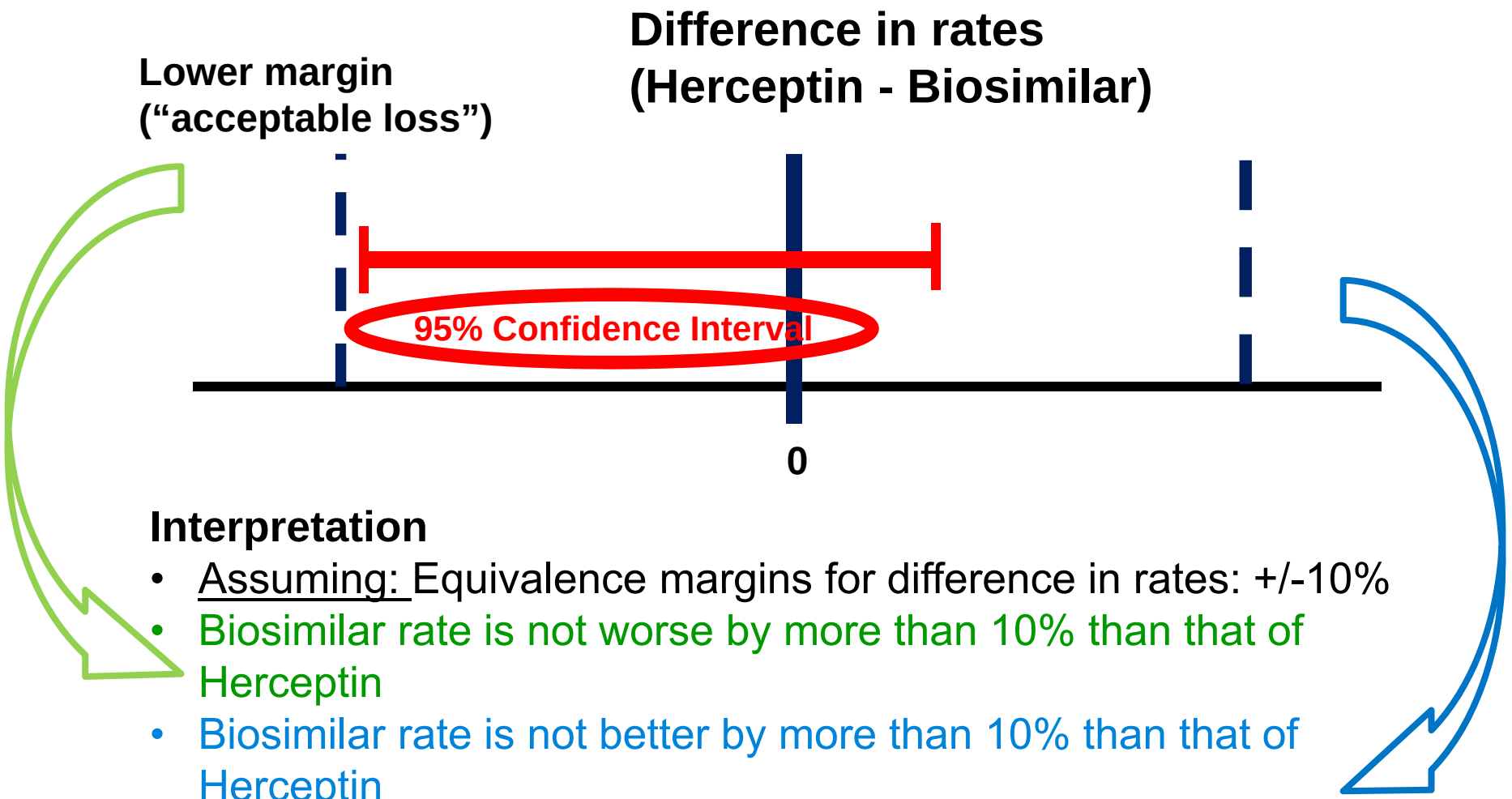
ABSTRACT **Aims:** Identify sensitive end points and populations for similarity studies of trastuzumab and biosimilar monoclonal antibodies. **Methods:** We performed meta-analyses of trastuzumab clinical trials data: overall response rate (ORR) and progression-free survival in metastatic breast cancer (MBC), and total pathologic complete response (tpCR) and event-free survival in the neoadjuvant setting. Fitted models predicted the maximum loss in long-term efficacy for different similarity trial designs. Immunogenicity rates were investigated in different early breast cancer (EBC) study phases. **Results:** Using the same equivalence margins for ORR (MBC) and tpCR (EBC), the predicted maximum loss in long-term efficacy with a biosimilar candidate versus the reference product is smaller for tpCR than for ORR. In EBC this predicted loss could be controlled with feasible patient numbers for a typical clinical trial. Analyses suggested that a treatment-free follow-up phase is preferable for immunogenicity characterization. **Conclusion:** Treatment of patients with neoadjuvant breast cancer represents a sensitive setting for establishing biosimilarity of efficacy and immunogenicity. tpCR is a sensitive end point in this setting to establish biosimilarity between a biosimilar candidate and its reference product.

Biosimilarity Equivalence trial



Equivalence trial: Biosimilar Candidate vs Reference Product

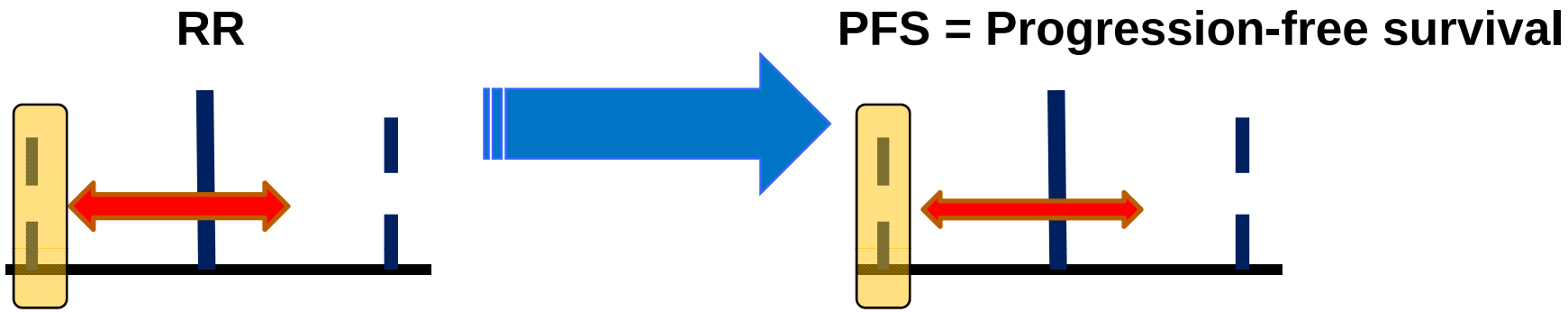
Case study trastuzumab: Equivalence trial



Interpretation

- Assuming: Equivalence margins for difference in rates: +/-10%
- Biosimilar rate is not worse by more than 10% than that of Herceptin
- Biosimilar rate is not better by more than 10% than that of Herceptin

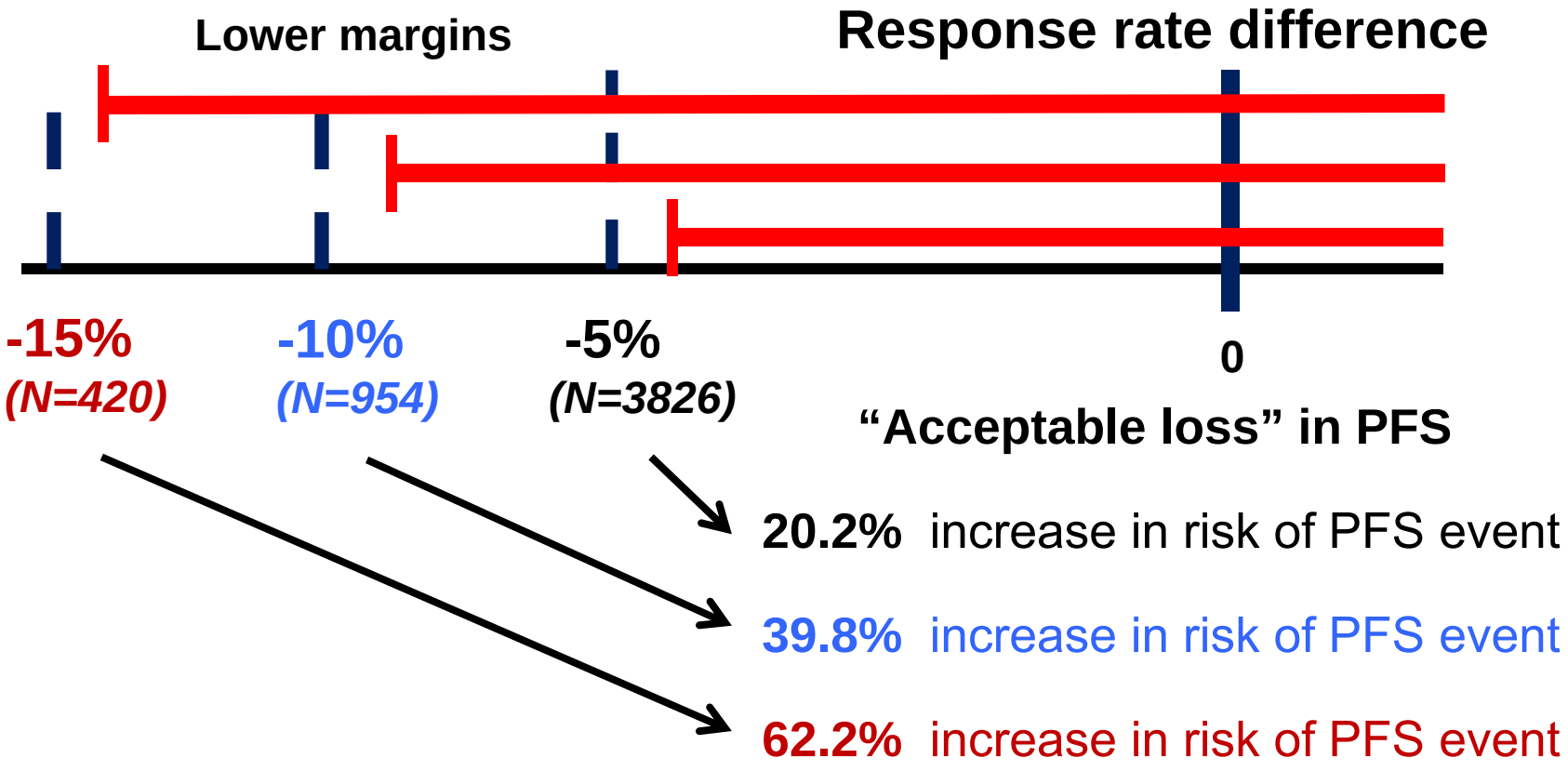
Case study trastuzumab: Equivalence trial MBC



- **Question:** What does the lower margin for RR tells us with respect to potential loss of long-term efficacy (PFS)?
- **Method:** Meta-analysis to estimate relationship of RR with PFS
  - –1276 patients: 8 trials with 2429 patients
- Relationship used to **"translate"** margin for RR into margin for PFS = "Acceptable loss" in long-term efficacy (PFS)

Case Study Trastuzumab: “Translation” MBC

- *8 trials with 2429 patients (randomized trial incl Herceptin+chemo arm)*



The percentage increase in long-term outcome (e.g. 39.8% for the 10% margin). This is the model outcome in terms of the hazard ratio which predicts the maximum loss in PFS when using the corresponding equivalence margins for ORR. The percentage 39.8% corresponds to a hazard ratio of 1.398 when comparing the biosimilar candidate to the reference product.

Case study trastuzumab: Conclusions for MBC

- A 15% and even a 10% equivalence margin results in a high potential loss in PFS
- High uncertainty in PFS makes extrapolation from MBC into EBC risky

- **Alternative approaches to establish clinical similarity?**

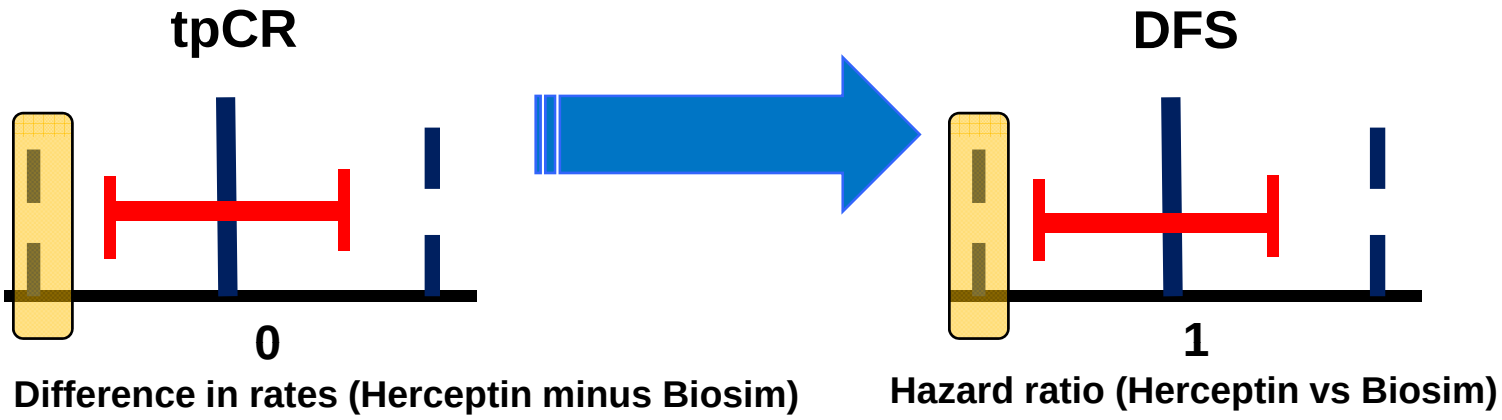
Case Study Trastuzumab:
Treatment Effect Size and Sensitivity of tpCR

	tpCR Overall Population *
Herceptin plus Chemotherapy	38 %
Chemotherapy	19 %
Effect Size	**19 %**

- tpCR differentiates more effective treatments from less effective ones
- supported by significant result in long-term outcome

*Gianni, Baselga, Lancet. 2010.

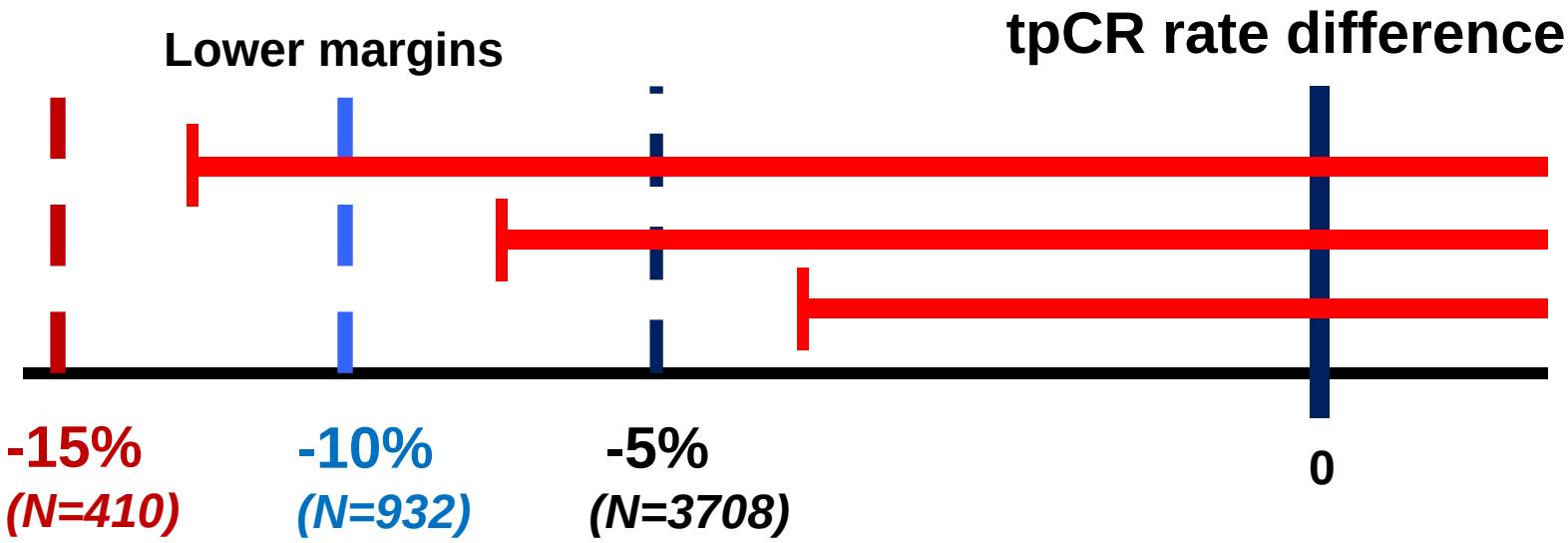
Case Study Trastuzumab: "Translation" neoadjuvant-adjuvant



- **Method:** Meta-analysis to estimate relationship of tpCR with DFS
  - 1276 patients: NOAH: Gianni (Lancet 2012), GeparQuattro: Minckwitz et al (in press Ann Oncol 2013), HannaH: Ismael (Lancet Oncol 2012)

- Relationship used to "translate" lower margin for tpCR into margin for DFS = "Acceptable loss" in long-term efficacy (DFS)

Case Study Trastuzumab:
"Translation" Neoadjuvant setting



"Acceptable loss" in DFS

9.8% increase in risk of DFS event

24.6% increase in risk of DFS event

44.3% increase in risk of DFS event

Case study trastuzumab: Conclusions Efficacy part

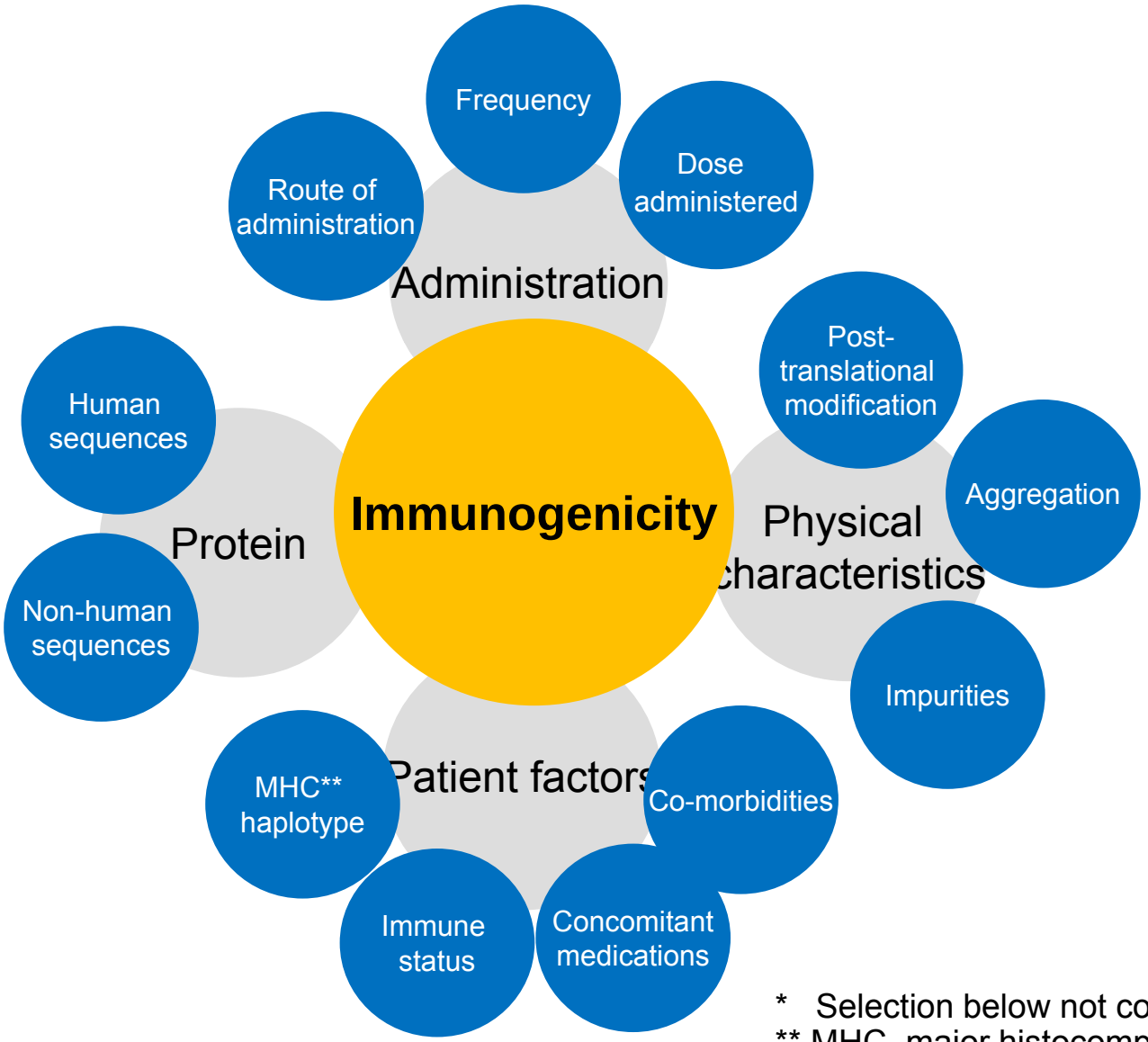
- Neoadjuvant-adjuvant is a sensitive setting with tpCR a sensitive endpoint to establish similarity
- For tpCR, feasible trial (10% margin, N=932) which controls “loss in long-term efficacy” (potential DFS risk increase 24.6%)
- The increase in risk is considerable lower as compared to the MBC setting with RR as an endpoint (PFS risk increase 39.8%)

Immunogenicity of Biotherapeutics

- One of the key factors that distinguishes biotherapeutic medicines from low-molecular-weight pharmaceuticals is their capacity to elicit an *immune response*
- Immunogenicity is the production of host antibodies directed against a therapeutic (anti-drug antibodies, ADA)
- Rates of immunogenicity vary by product and condition of use (from <1% to >50%)[1,2]
- ADAs may have no clinical impact, may impact bioavailability, or may impact safety and efficacy[1,2,3]

1. Koren, E., et al. (2002). "Immune Responses to Therapeutic Proteins in Humans - Clinical Significance, Assessment and Prediction." Current Pharmaceutical Biotechnology **3(4): 349-360.**
2. Purcell, RT and Lockey, RF. (2008). "Immunologic Responses to Therapeutic Biologic Agents." Journal of Investigational Allergololgy & Clinical Immunology **8(5): 335-342**
3. Chirmule, N., et al. (2012). "Immunogenicity to Therapeutic Proteins: Impact on PK/PD and Efficacy." The AAPS Journal **14(2): 296-302.**

Immunogenicity is influenced by a wide range of different factors*



* Selection below not complete
** MHC, major histocompatibility complex

Immunogenicity of therapeutic Mabs

Antibody Class	Therapeutic Area	MAb	(Main) Indication	Frequency [Overall, w, w/o Co-Medication]	Consequences: (…): Trend; (…, Single Cases): Influence in Single Patients		
					Pharmacokinetics	Efficacy	Safety
Human	CID	Ad	[Overall]	[b]	CL ↑	Efficacy ↓	No apparent effect
			Rheumatoid arthritis	5.5%, 0.6% w, 12.4% w/o MTX			
			PJIA	15.8%, 5.9% w, 25.6% w/o MTX			
			Psoriatic arthritis	10.1%, 7.1% w, 13.5% w/o MTX			
			Ankylosing spondylitis	8.3%, 5.3% w, 8.6% w/o MTX			
			Crohn's disease	2.6%			
			Psoriasis	8.4%			
		Us	Plaque psoriasis	5%[b]	(CL ↑)	(Efficacy ↓)	No apparent effect
	Onc/Haem	Pa	Colorectal cancer	0.2, 1.6%[b] Up to 3.8%, persistent 2.0%[a]	No apparent effect	No apparent effect	No apparent effect
Fusion proteins	CID	Ab	Rheumatoid arthritis	2.8%, up to 7.4%[b, a]	No apparent effect	Not yet finally evaluated	Not yet finally evaluated
		Et	[Overall]	[b]	NA	No apparent effect	No apparent effect
			Rheumatoid arthritis	6%			
			Psoriatic arthritis	7.5%			
			Ankylosing spondylitis	2%			
			Plaque psoriasis	7%			
			Psoriasis	Up to 9%			

Based on information from the European Public Assessment Reports; mAbs are abbreviated to their first two letters, cf. Table 2.
'Marketing authorisation suspended by European Commission.
References: a: scientific discussion/assessment report; b: product information.
AR/HSR: administration-related/hypersensitivity reactions; B-CLL: B-cell chronic lymphocytic leukemia; CID: chronic inflammatory diseases; CL: clearance; IST: mmunosuppressive therapy; MTX: methotrexate; NA: not available, no statement; Onc/Haem: oncology/haematology; PJIA: polyarticular juvenile idiopathic arthritis; w, w/o: with, vithout.

***R. Niebecker et. al Current Drug Safety*, 2010, *5,* 275-286 275**
Safety of Therapeutic Monoclonal Antibodies

Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner

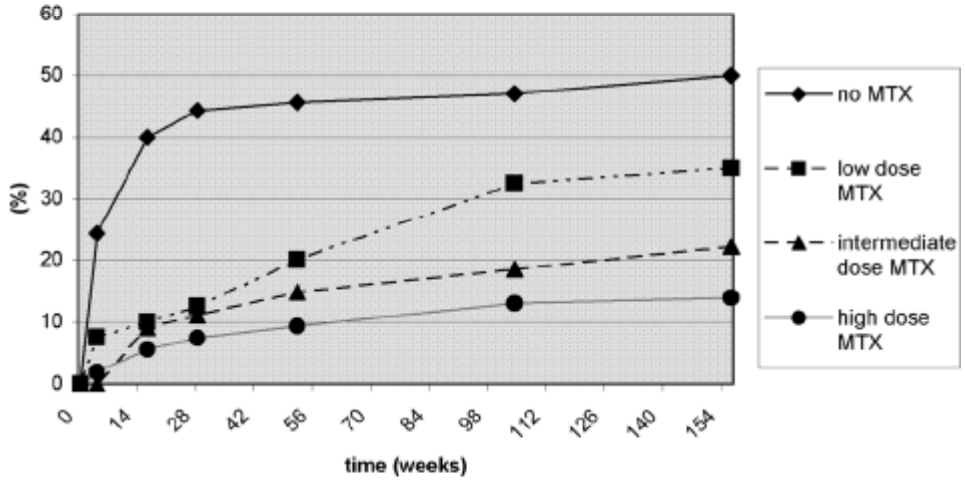
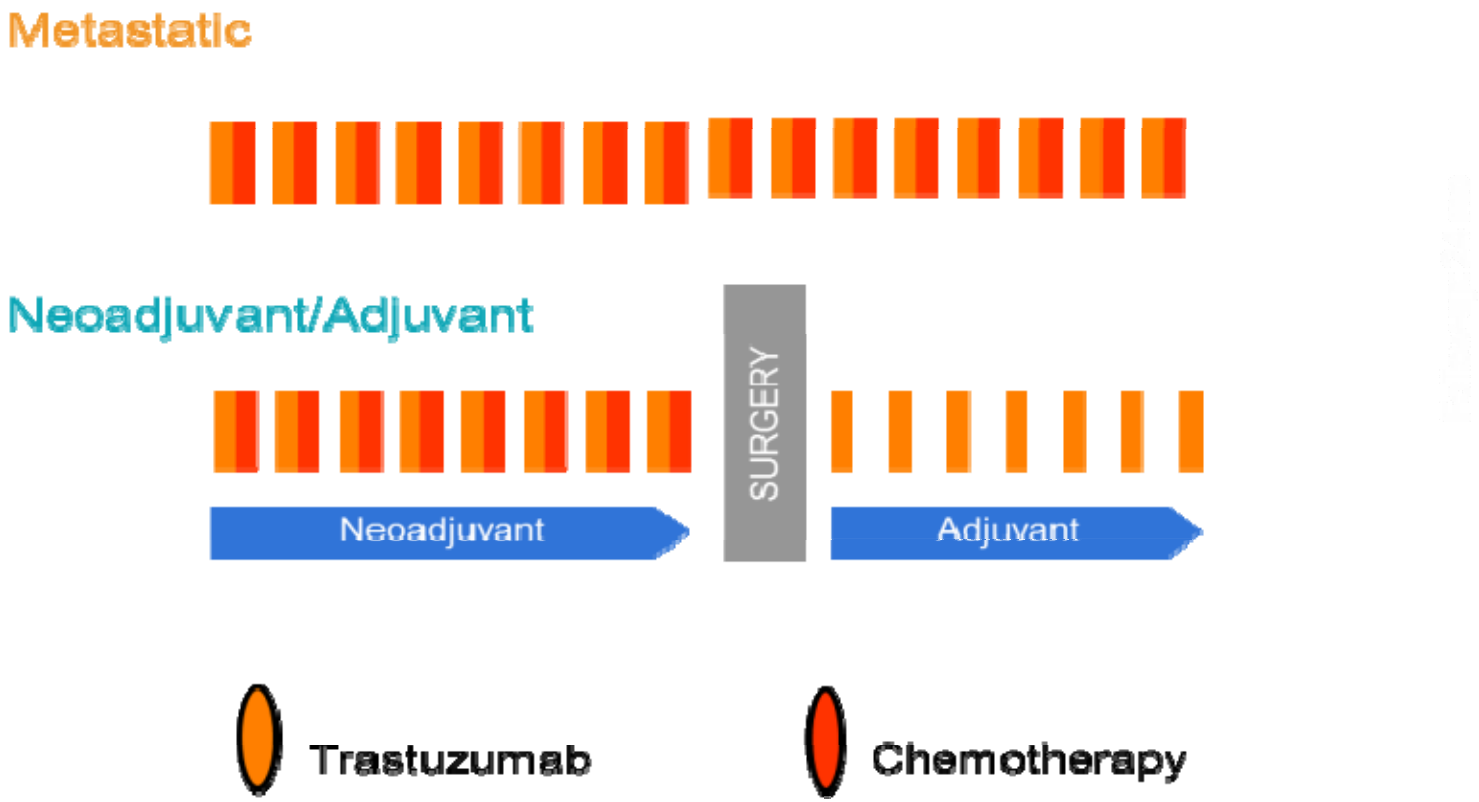


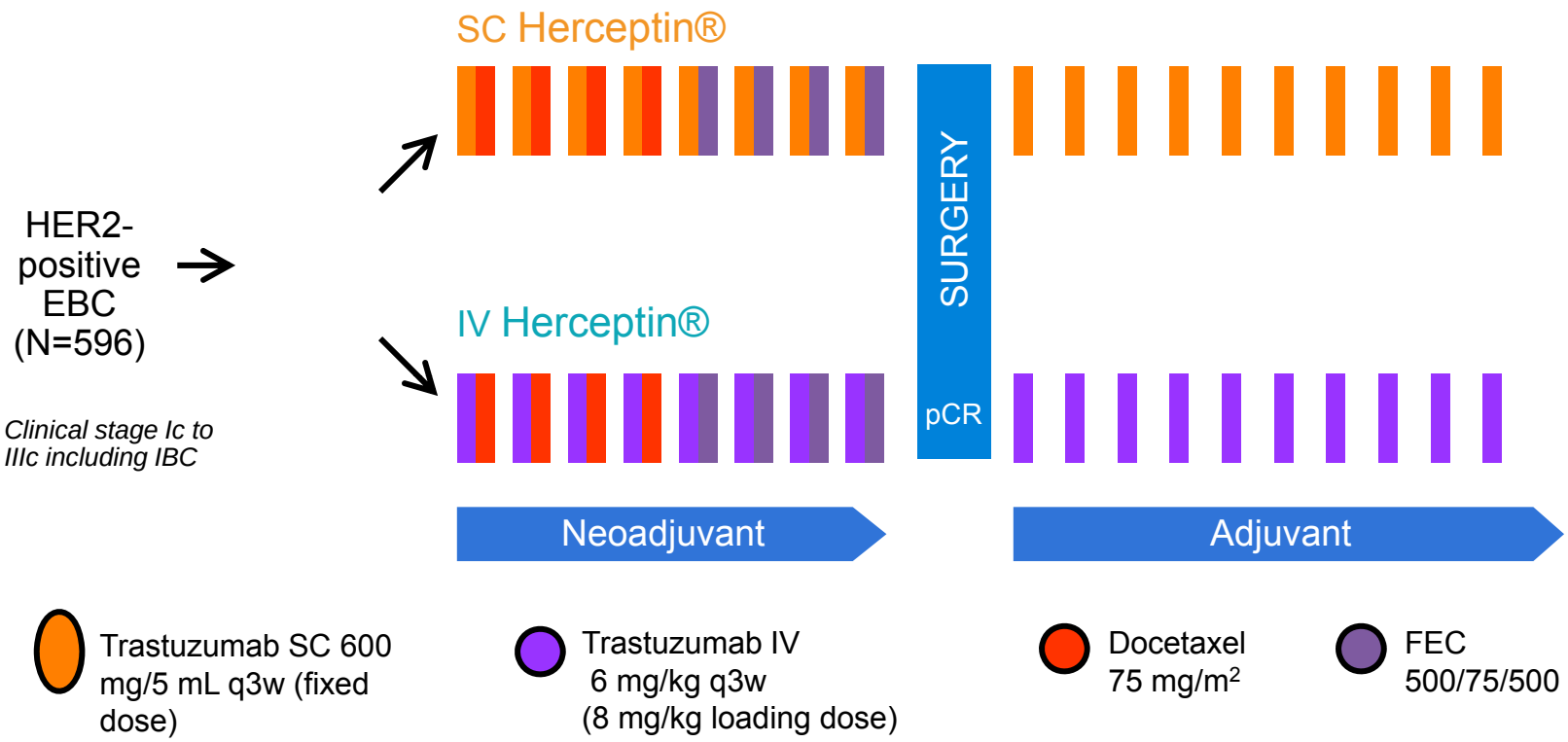
Figure 1 Percentage of patients developing antiadalimumab antibodies (AAA) per baseline methotrexate (MTX) dose group. No MTX (0 mg/week, n=70), low dose MTX (5–10 mg/week, n=40), intermediate dose MTX (12.5–20 mg/week, n=54), or high dose MTX (≥22.5 mg/week, n=108).

Case study trastuzumab:
What is the most sensitive indication/patient population to establish similarity in immunogenicity

Trastuzumab treatment regimens are different in different patient populations



Case study trastuzumab: HannaH Phase III Study



Objective:

Show non-inferiority of SC vs. IV based on co-primary endpoints

- PK: observed trastuzumab C_{trough} pre-dose Cycle 8
- Efficacy: pathological complete response (pCR) in the breast

FEC, 5-fluorouracil, epirubicin and cyclophosphamide. IBC, inflammatory breast cancer

Case study trastuzumab: Sensitivity of the neoadjuvant-adjuvant setting to detect differences in immunogenicity

- Observed ADA rates (anti-drug antibody against Herceptin)*:
  - **Herceptin IV: 7.1% (21/295)**
  - **Herceptin SC: 14.6% (43/295)**
- **Sensitive setting**: Difference between drugs (formulations) could be found if there is one
- **No correlation of ADA to efficacy/safety/PK was detected for Herceptin**

*Definition: ADA rates (all patients who tested positive for ADAs at least once post-baseline)

Case study trastuzumab: Key conclusions on extrapolation of immunogenicity data

- Immunogenicity of a biosimilar trastuzumab candidate has to be thoroughly investigated and characterized in the most sensitive setting prior to approval.

- **The adjuvant setting is considered to be sensitive** and allows the inclusion of data from **a treatment-free follow-up phase** which **is crucial for the comprehensive characterization of the immune response of trastuzumab**.

- Therefore **extrapolation of immunogenicity data** obtained in the **EBC setting to MBC is possible** while **extrapolation of immuno-genicity data from MBC to the EBC population represents a major risk** if no safety and efficacy data are available.

EBC = Early Breast Cancer; MBC = Metastatic Breast Cancer

Celltrion's CTP-6 Approval in Korea

A Double-blind Randomised, Parallel Phase I/IIb Study to Evaluate Initial Safety and Efficacy, Comparative Pharmacokinetics and Immunogenicity for CT-P6 and Herceptin in Metastatic Breast Cancer	
Number of pts.	174
Patient population	mBC patients
Design	Randomized, double-blind; CT-P06 vs. Herceptin
Primary end point	PK parameters
Secondary end point	PK data, safety and efficacy
Study Start	Jan 2010; Primary completion – Dec 2011; Study completion – June 2013
No. of sites; Regions included	Multicenter trial (Asia, East and West Europe, LatAm)
Key Partnerships	Hospira

Source: http://clinicaltrials.gov/ct2/show/NCT01084863?term=CT-P6&rank=1

Celltrion's CTP-6 Approval in Korea

A Double-blind, Randomised, Parallel Group, Phase III Study to Demonstrate Equivalent Efficacy and Comparable Safety of CT-P6 and Herceptin, Both in Combination with Paclitaxel, in Patients with Metastatic Breast Cancer	
Number of pts.	383
Patient population	mBC patients
Design	Randomized, double-blind; CT-P06 vs. Herceptin
Primary end point	To Compare Efficacy
Secondary end point	Efficacy and safety parameters
Study Start	June 2010; Primary completion – Dec 2011; Study completion – June 2013
No. of sites; Regions included	Multicenter trial (Asia, East and West Europe, LatAm)
Key Partnerships	Hospira

Source: http://clinicaltrials.gov/ct2/show/NCT01084863?term=CT-P6&rank=1

Biocon/Mylan Approval of Trastuzumab in India

Comparative PK, Efficacy, Safety and Immunogenicity evaluation of Bmab-200 versus Herceptin, both in combination with Docetaxel in patients with Her2+ Metastatic Breast Cancer: A Double Blind, Randomised, Active Control, Parallel assignment, Comparative Phase III, Clinical Trial	
Number of patients	132
Patient population	Metastatic breast cancer
Design	Randomised, double blind, parallel arm, active comparator
Primary and secondary endpoints	• The equivalence of single-dose pharmacokinetics between Bmab-200 and Herceptin in terms of AUC0-t and Cmax • Overall response rate (ORR) over 8 cycles of combination chemotherapy with docetaxel • The multiple-dose pharmacokinetic parameters of Bmab-200 and Herceptin • Safety and immunogenicity
Study start	Q3 2011
Estimated completion	Q4 2013 (completed Aug 2013)
No. of sites/regions	22 sites in India

Source: http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=3062&EncHid=&userName=biocon

Biocon/Mylan global development of trastuzumab

A multicenter, double-blind, randomized, parallel-group, phase III study to compare the efficacy and safety of Hercules versus Herceptin® in patients with HER2+ metastatic breast cancer	
Number of patients	470
Patient population	Metastatic breast cancer
Design	Randomised, double blind, parallel arm, active comparator
Primary endpoint	Overall response rate (ORR) where response is defined as a complete or partial remission according to RECIST 1.1 based on central tumor evaluation
Study start	December 2012
Estimated completion	December 2014
No. of sites/regions	Belarus, Bosnia and Herzegovina, Bulgaria, Czech Republic, Georgia, Germany, Hungary, India, Malaysia, Morocco, Philippines, Poland, Romania, Russian Federation, Serbia, Slovakia, South Africa, Thailand, Tunisia, Turkey and Ukraine

Mylan/Biocon are conducting a separate global Phase III trial for their trastuzumab biosimilar in mBC patients for European filing; brand name HERCULES®

Source: https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-001965-42/HU

Amgen's global development for a trastuzumab biosimilar

Randomized, single dose, parallel group, bioequivalence study, comparing trastuzumab (Synthon) to Herceptin® infusion in healthy male volunteers following a placebo-controlled dose escalation period	
Number of pts.	118
Patient population	Healthy males, 18-45 years of age
Design	Randomised placebo-controlled double blind dose escalation & parallel laboratory blinded bioequivalence
Primary end point	• PK-profile: concentration - sampling at 0.75, 1.5, 2, 3, 4, 5, 6, 8, 24, 48, and 96 hours post dose, and 8, 14, 21, 28, 35, 42, 49, and 63 days post dose (to demonstrate bioequivalence). • Safety and tolerability: general chemistry/haematology and urinalysis, cardiac markers, echocardiography, ECG, observation and questions, vital signs
Secondary end point	PK-profile: concentration - sampling at 0.75, 1.5, 2, 3, 4, 5, 6, 8, 24, 48, and 96 hours post dose, and 8, 14, 21, 28, 35, 42, 49, and 63 days post dose (to evaluate pharmacokinetic parameters).
Study Start/End date	Jan 2011; End date Jan 2012
No. of sites; Regions included	Denmark, Netherlands

clinicaltrials.gov listing

Amgen's global development for a trastuzumab biosimilar

A Randomized, Double-Blind, Phase 3 Study Evaluating the Efficacy and Safety of ABP 980 Compared with Trastuzumab in Subjects with HER2 Positive Early Breast Cancer	
Number of pts.	556 **Updated Jan '14 to 808 pts**
Patient population	early breast cancer patients
Design	Double Blind, Randomized, Parallel-Group, two arm trial
Primary end point	Risk ratio (RR) of the incidence of pathologic complete response (pCR) in breast tissue and axillary lymph nodes
Secondary end point	• Risk ratio (RR) of pCR in breast tissue • Risk ratio (RR) of pCR in breast tissue and axillary lymph nodes and absence of Ductal Carcinoma In Situ (DCIS)
Study Start	Q2 2013; Study end date: Q3 2015
No. of sites; Regions included	Belarus, Brazil, Bulgaria, Canada, Czech Republic, Germany, Greece, Hungary, Italy, Mexico, Peru, Poland, Romania, Russia, Serbia, Slovakia, South Africa, Spain, Ukraine and UK

***Source*:** European trial registry https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-004319-29/DE

Summary

- **The application of proper risk mitigation strategies during the development and marketing of biosimilar products is fundamental.**
- **Only a highly similar product should be allowed to enter the next stages of the similarity assessment e.g. pre-clinical and clinical assessments as it will allow for robust regulatory decisions .**
- **Comparative clinical testing is a key part of the risk mitigation strategies and has to be done in the relevant setting(s) most sensitive to detect potential differences in safety, efficacy and immunogenicity.**
- **Given the the fact that clinical studies for a biosimilar are abbreviated and not done in all indications a proper RMP as well as active pharmacovigilance are an essential part of the biosimilar concept.**
- **Unique product identification is a must in that context.**

Establishing biosimilarity is a challenge requiring new thinking in many areas and leaving behind old *generic* habits

Peter the Great
(*1672 †1725)


Thank You !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