Your clinical gateway to Europe

Clinical Trials for Biosimilars- Principles & Challenges

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AGENDA

- Biosimilars - still a new paradigm
- Regulations – facing increasing complexity
- Clinical trial challenges – Design and Effect
- Summary and Outlook

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Biosimilar developments

EUROPE currently largest biosimilar market

First Biosimilar was approved in Europe in 2006 (Omnitrope® developed by Sandoz, a Biosimilar of Genotropin® from Pfizer, rhGH)

Since then 17 Biosimilars have gained Marketing Authorization in Europe

Main Products:

- EPO to treat anemia after renal dialysis
- G-CSFs for lowered white blood cell counts after chemotherapy
- Human Growth Hormones

US market to evolve through government initiative for health care reform, implementation of biosimilar guideline 2013

Pharmemerging Markets on a fast track through own regulatory pathways, developing biosimilars for local and global markets

Expectations towards Biosimilars

Provide cost savings
In health care costs

Increase patient access

Biosimilars 20-30% price reduction than Reference product (generics 70%)

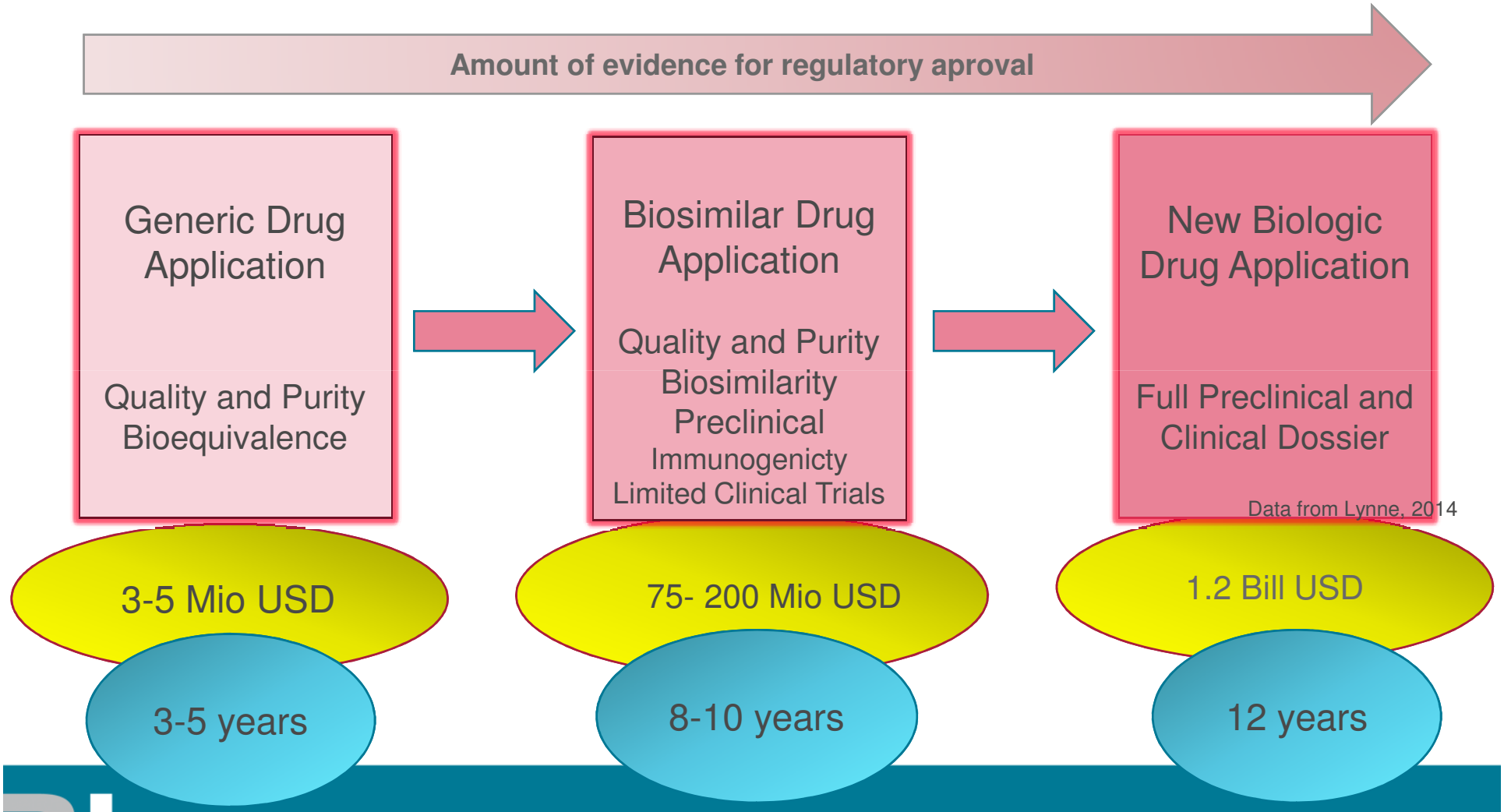
Germany: 60 Mio EUR savings due to price reduction within first 12 months after entry of Biosimilar Epythroproietin

Top selling biologics (Hercepetin, Enbrel, Humalog etc) loose patent protection at the end 2020

Increasing development of regulatory pathways to develop Biosimilars

Increasing competition to develop Biosimilars, Key players, national companies

Biosimilar – a complex development process



Different Names same Meaning - same requirements

Europe (EMA): (2005/2013)
Similar biological medicinal product

WHO: Similar biological product (SBP) /Reference Biological Product (RBP)

USA (FDA): Biological product/Biosimilar

National Regulation: terms can vary (e.g.follow-on biologic)

Common Biosimilar concept:
To prove (highly) similarity to a Reference Product

Scientific principle
Quality characteristics
(analytical,physicochemical,manufacturing)
Non clinical data
Safety and efficacy

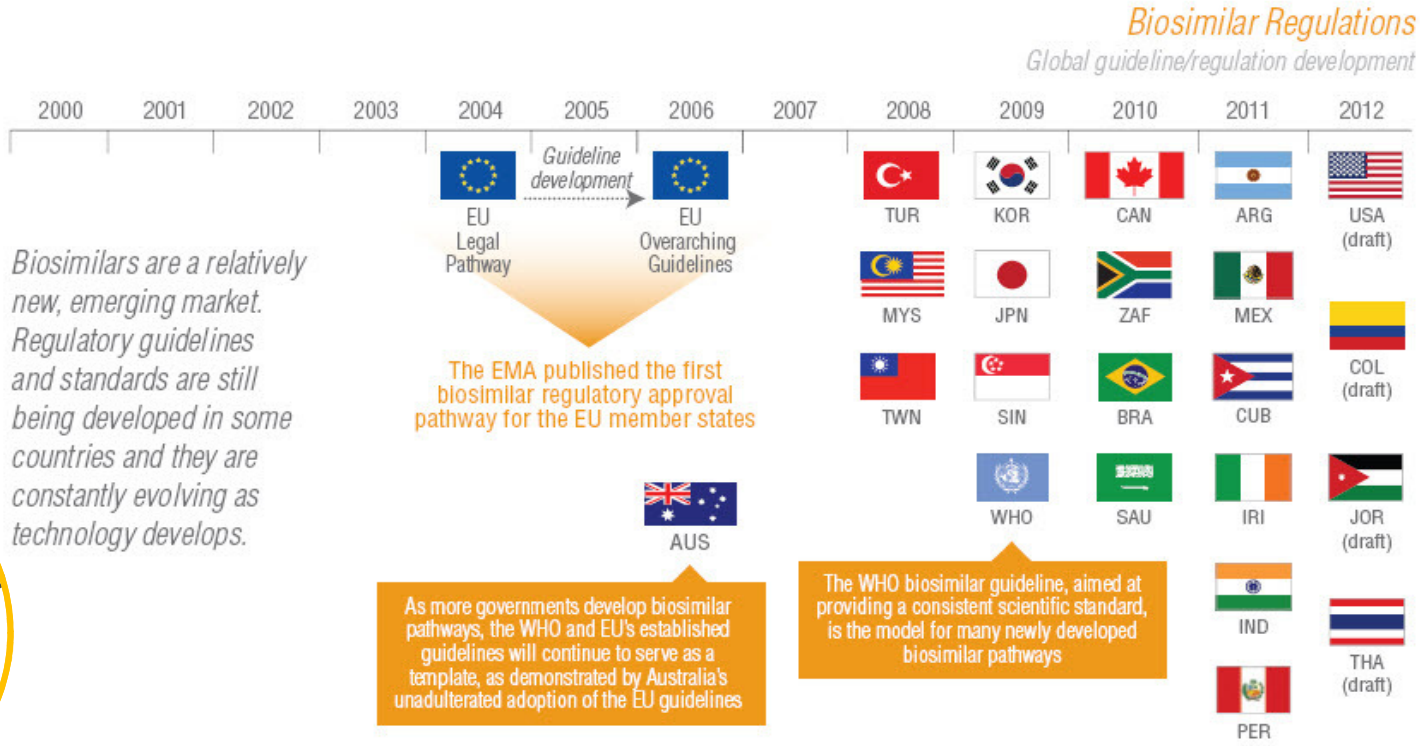
- At any step differences must be explained and justified, might require additional data (e.g. safety), head to head comparison
- If not similar to the reference product could lead to stand alone product development

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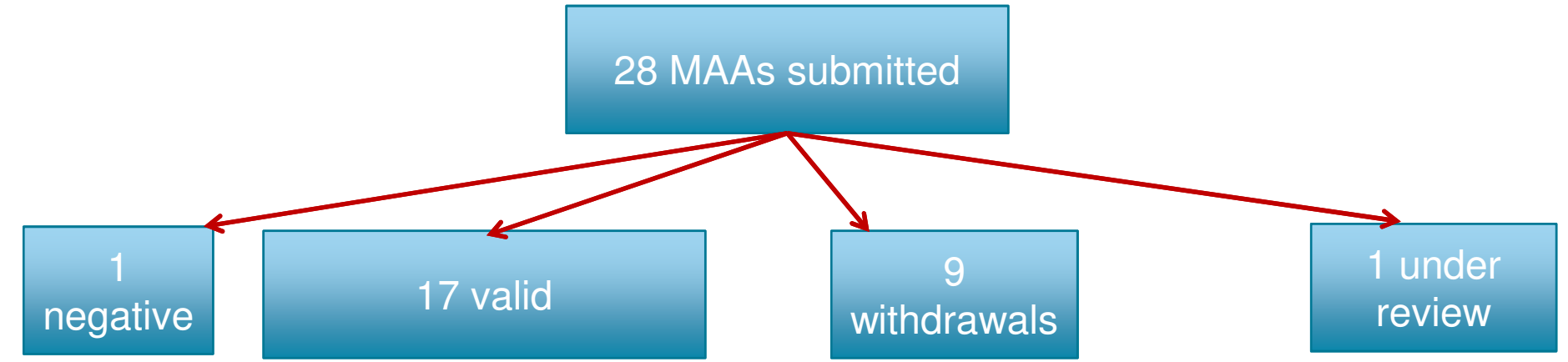
Worldwide Biosimilar regulatory pathways

2014
EMA revised guideline on Biosimilars containing recombinant proteins as active substance



Amgen: Biologics and Biosimilars

Biosimilar Marketing Authorisations EMA 2013



Interferon alfa

Somatropin (1)
Epoetin (5)
Filgrastim (7)
Infliximab (2)
Follotropin alfa (2)

Insulin (6)
Epoetin (1)
Filgrastim (1)
Somatropin (1)

Insulin glargine (1)

General Requirements to prove similarity

EMA

- Quality (chemistry, manufacturing and control, physiochemical properties, Impurities
- Comparability-data
- Non-clinical
- Clinical

WHO

- Quality
- Analytical
- Non-clinical evaluation
- Clinical evaluation

FDA

- Analytical
- Non-Clinical
- Clinical pharmacology
- Clinical Safety & Efficacy

Stepwise approach – Product and process unterstanding for every comparability exercise
Clinical studies with test product of final manufacturing process
FDA: „totality of the evidence approach“

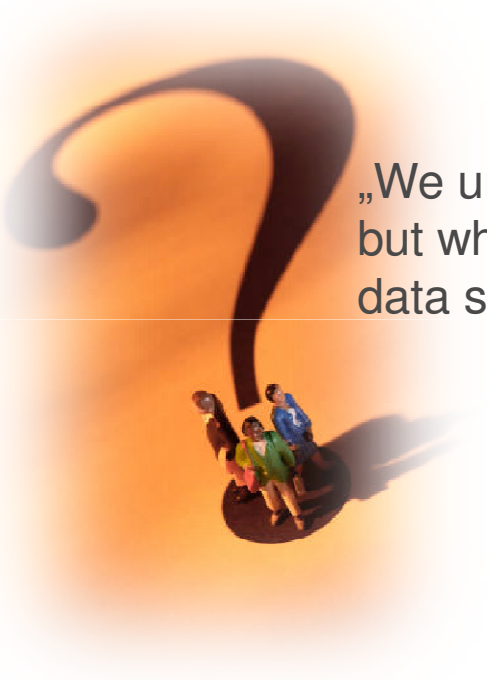
Reference Product

- Reference product needs to be authorized in the country
- Must always be the same
- Chosen reference product must be suitable to support the application for MA (completeness of data)
- Dosage form and route of administration of the Biosimilar and Reference Product must be the same
- A Biosimilar cannot be considered a Reference Product
- Limited clinical data of Reference Product might need to require additional data with Biosimilar

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Cinical trials - what is needed



„We understand the need of PK/PD studies, but why clinical trials if quality and non-clinical data show high similarity?“

„Wouldn`t be a safety study enough?“

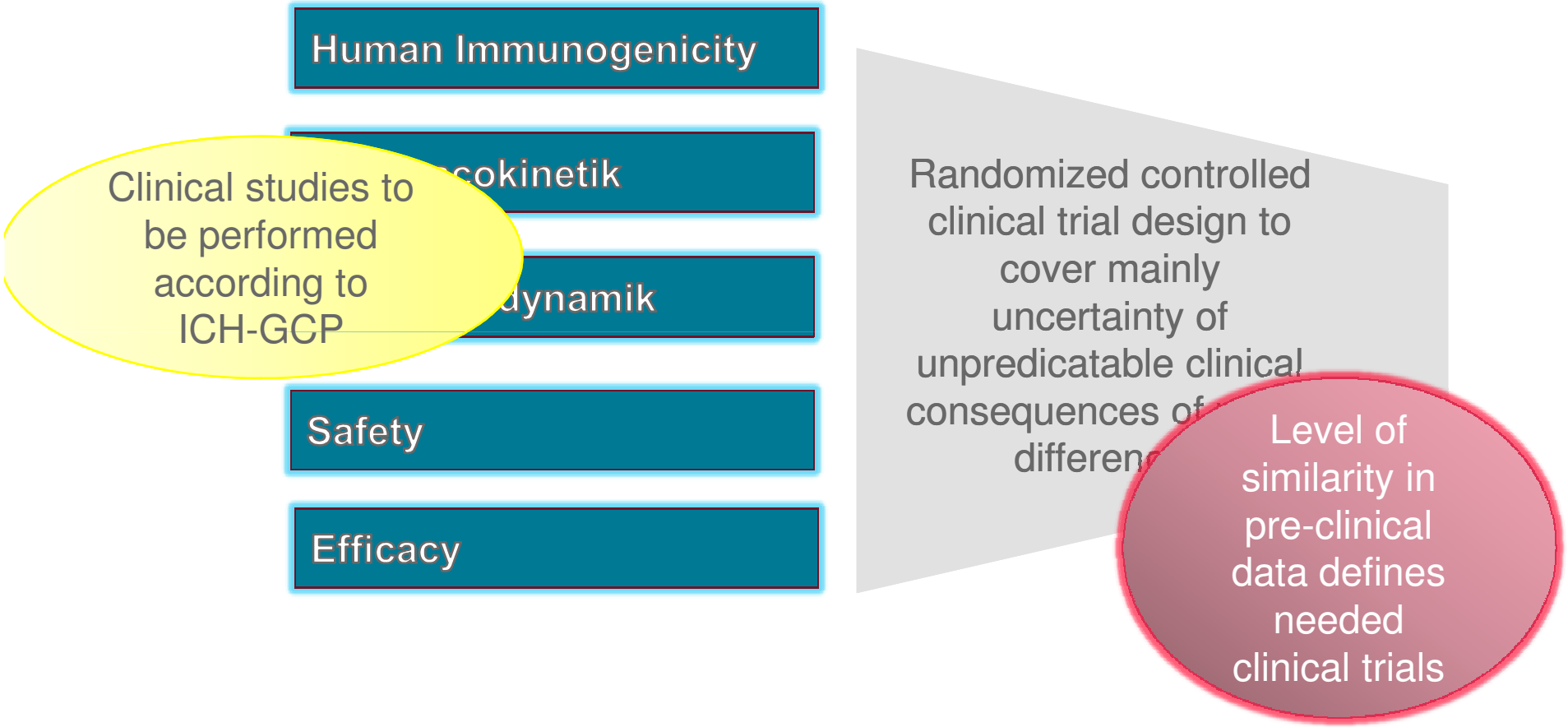
What needs to be tested?

- Patient benefit
- Therapeutic effect
- Safety
- Efficacy

- Human Immunogenicity
- Pharmacokinetik
- Pharmacodynamik
- Adverse event profile

Might be requested as post marketing authorization trial

What needs to be evaluated?



General Requirements for clinical trials

- Overall: No clinically meaningful differences between biosimilar and the reference product for safety and efficacy

- Stepwise approach - PK/PD Data – Efficacy clinical trials
- Scienfic proven statistical concept to show similarity
- Sensitive endpoints to detect clinically meaningful differences in safety and efficacy between products
- Clinical trials to be assessed on case by case basis, depending on residual uncertainty

PK/PD studies

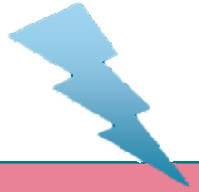
- Stepwise procedure before efficacy trials
- PK comparison of Reference and Biosimilar - single dose cross over study to characterize absorbtion, bioavailabiltiy and also elimination characteristics for products with short half life
- Parallel design if longer half-life
- Dose to be sensitiv to detect differences
- Healthy volunteers if possible (AEs, risks) – homogenous patient population
- Add PD markers to PK studies
- Comparative PK/PD studies

Efficacy Trial design – Equivalence testing

Randomized controlled clinical trials – gold standard – hypothesis testing

Test drug does not show better or less efficacy
Null hyothesis: treatments are not equivalent
Alternative hypothesis: they are equivalent

Largest difference in efficacy that has no clinical relevance (lower and upper equivalence margin), two sided test within 95% CI



Finding of superiority leads to failure of equivalence trial

EMA, WHO and FDA generally recommend equivalence trials

Clinical trial design

Clinical endpoints

- Are not similar to endpoint of reference product (patient benefit)
- Need to detect potential differences in efficacy, not demonstrating efficacy
- Need to measure drug activities
  - e.g.Overall survival vs reduction/change of tumor mass (more sensitive)
- Use of Pharmacodynamik endpoints e.g. assessment of changes in tumor markers
  - Depend on understanding of mechanism of action, availability of PD measures and correlation with clinical outcomes

Individual definition of efficacy endpoint for each class of Biosimilar

Safety assessments - Immunogenicity

- Animal data not predictive for human immune response
- Refers to generation of Antibodies and neutralizing antibodies (NAbs)when using biologic drugs → to loss of efficacy (Nabs)
  → Autoimmune reaction to an endogenously produced protein
- To be investigated in patient population with hight risk immune response/immun-related adverse event
- Sponsor to define and justify antibody testing strategy
- Duration of observation depend on Antibody development time
- Post-marketing studies for further characterization of immunogenicity
- Risk Management Plan

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Summary and Outlook

- Agents with increased complexibility will enter global markets (e.g. monoclonal antibodies)
- Any difference between Biosimilar and Originator should always be explained and justified with perspective to clinical relevance; scientific proven concept
- In depth understanding of mechanism of action and manufacturing process needed



- Increase complexity of biologics should not lead to increase of costs to develop Biosimilar
- More data needed to understand longterm biosimilarity (Pharmacovigilance)
- Set of biosimilar class specific efficacy endpoints needed


Dhanyavaad !
Thank you !