2nd Annual Biosimilars Forum

12 years of biosimilars in Europe: What is the exposure and response in our learning curve?

2nd Annual Biosimilars Forum
Statistical and Regulatory Perspectives in Bio- and Nanosimilar Development
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Disclaimer

- *I attend this conference as an individual expert, and do not represent the CHMP or the Austrian Medicines Agency*
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Overview

- The biosimilar regulatory framework in Europe
- Approved biosimilar products
- General aspects of biosimilar development
  - Changes in requirements at general, quality, (non)clinical level
  - General considerations on extrapolation
  - Relevant factors for generation of clinical data
- Tailored evidence for biosimilar products
  - Less complex biosimilars
  - Highly complex biosimilars
  - Orphan biosimilars
  - Locally acting biosimilars
- Summary and outlook

Legal basis for biosimilars in Europe

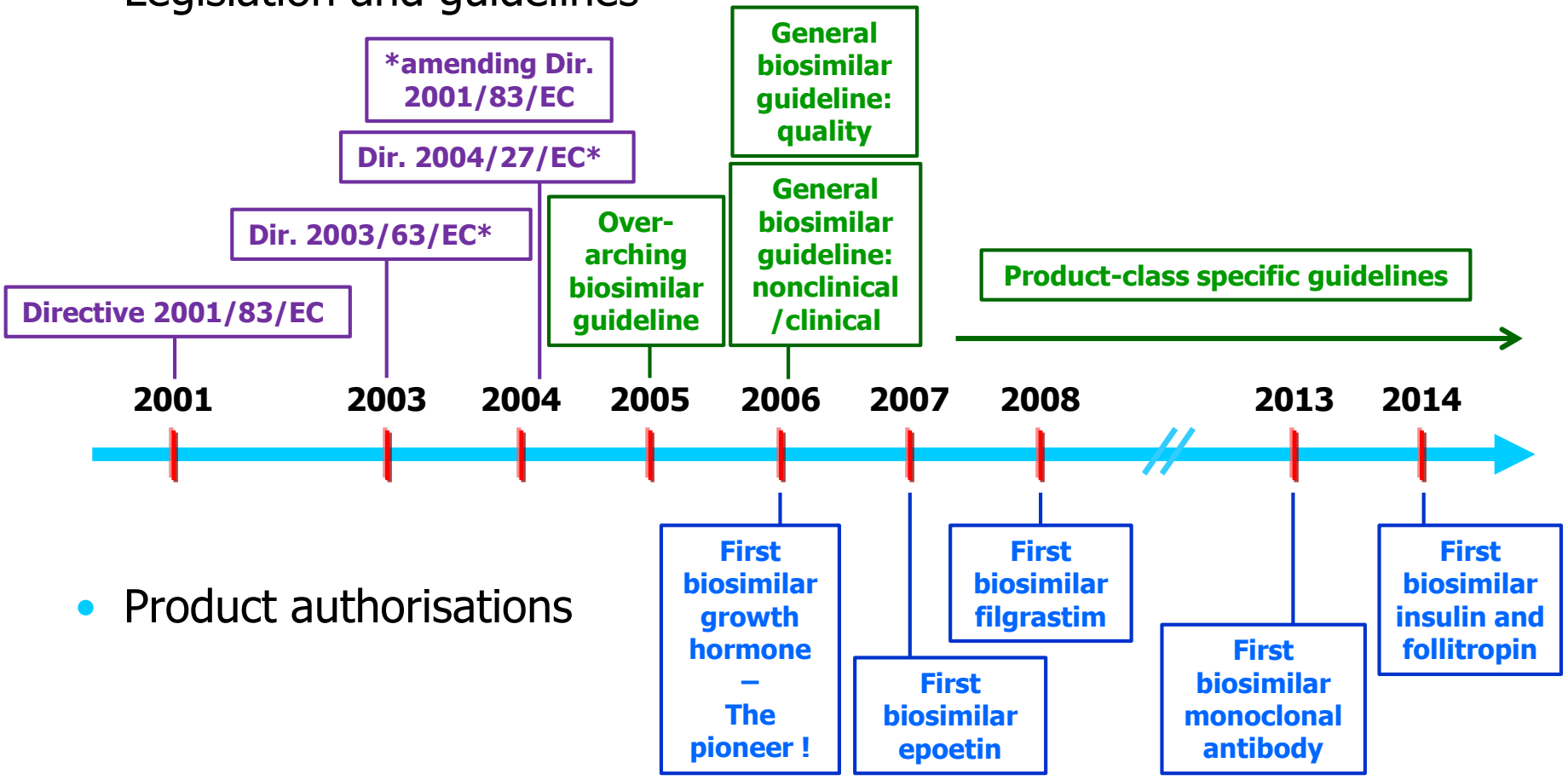
Directive 2001/83/EC (as amended in 2004)

- Article 10: „**Generics**" and „**biosimilars**"
  - Article 10(2a): *„Generic medicinal product" shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, ..."*
  - Article 10(4): *„Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided."*

Biosimilar framework over time

Evolution of biosimilars in the EU

- Legislation and guidelines



- Product authorisations

EMA Biosimilar Guidelines

GL on Similar Biological Medicinal Products („Overarching GL") **revised**

GL on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance („General GLs")

Quality Issues **revised**

Non-Clinical / Clinical Issues **revised**

"ANNEX GUIDELINES" (product class specific)

Epoetin	G-CSF	Somatropin	Insulin	Inter-feron α	LMW Heparin	mAbs	FSH	Inter-feron β
	under rev.		**revised**	under rev.	**revised**			

OTHER RELEVANT GUIDELINES

Comparability – manufact. change	Immunogenicity proteins	Immunogenicity mAbs	Comparability – manufact. change, (non)-clinical
	under rev.		

Biosimilar products in EU (as of Sept 2017)

36 products for 12 reference products are **on the market** (39 authorised)

INN	Name	MAH	Status	INN	Name	MAH	Status
Somatropin	Omnitrope	Sandoz	A	**Etanercept**	Benepali	Samsung	A
	Valtropin	Biopartners	W		Erelzi	Sandoz	A
Epoetin alfa	Abseamed	Sandoz	A	**Enoxaparin Na⁺**	Inhixa	Techdow	A
	Binocrit	Sandoz	A		Thorinane	Pharmathen	A
	Epoetin Alfa Hexal	Hexal	A				
Epoetin zeta	Retacrit	Hospira	A				
	Silapo	Stada	A				
Filgrastim	Biograstim	ABZ-Pharma	W	**Rituximab**	Truxima	Celltrion	A
	Filgrastim ratiopharm	Ratiopharm	W		Rixathon	Sandoz	A
	Ratiograstim	Ratiopharm	A		Riximyo	Sandoz	A
	Tevagrastim	Teva	A		Blitzima	Celltrion	A
	Filgrastim Hexal	Hexal	A		Ritemvia	Celltrion	A
	Zarzio	Sandoz	A		Rituzena	Celltrion	A
	Nivestim	Hospira	A				
	Grastofil	Apotex	A				
	Accofil	Accord	A				
Follitropin alfa	Ovaleap	Teva	A	**Teriparatide**	Movymia	Stada	A
	Bemfola	Finox Biotech	A		Terrosa	Gedeon Richter	A
Infliximab	Inflectra	Celltrion	A	**Adalimumab**	Amgevita	Amgen	A
	Remsima	Hospira	A		Solymbic	Amgen	A
	Flixabi	Samsung	A		Imraldi	Samsung	A
Insulin glargine	Abasaglar	Eli Lilly	A	**Insulin lispro**	Insulin lispro	Sanofi Aventis	A
	Lusduna	MSD	A				

Experience with approved biosimilars

- More than **10 years of experience** with biosimilars revealed no problematic findings as regards efficacy or safety
  - Largest records available on erythropoetin and filgrastim
    - Several post-marketing studies confirmed their efficacy and safety
  - No reports of lower efficacy or increased adverse events
  - No differences in occurrence of ADAs
  - Shorter but so far reassuring records with other biosimilar molecules
- Good experience also with **extrapolation**
  - Both erythropoetin and filgrastim are well characterizable proteins
    - Acting through the same mode of action in different indications
  - For monoclonal antibodies more difficult but yet manageable

Biosimilarity in immunogenicity

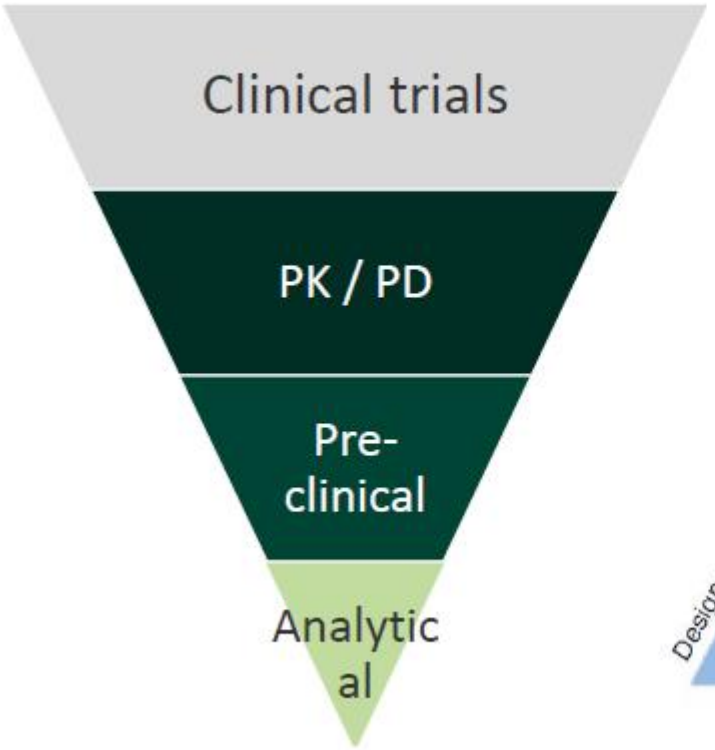
Antibody Frequency for Biosimilar (presubmission studies)

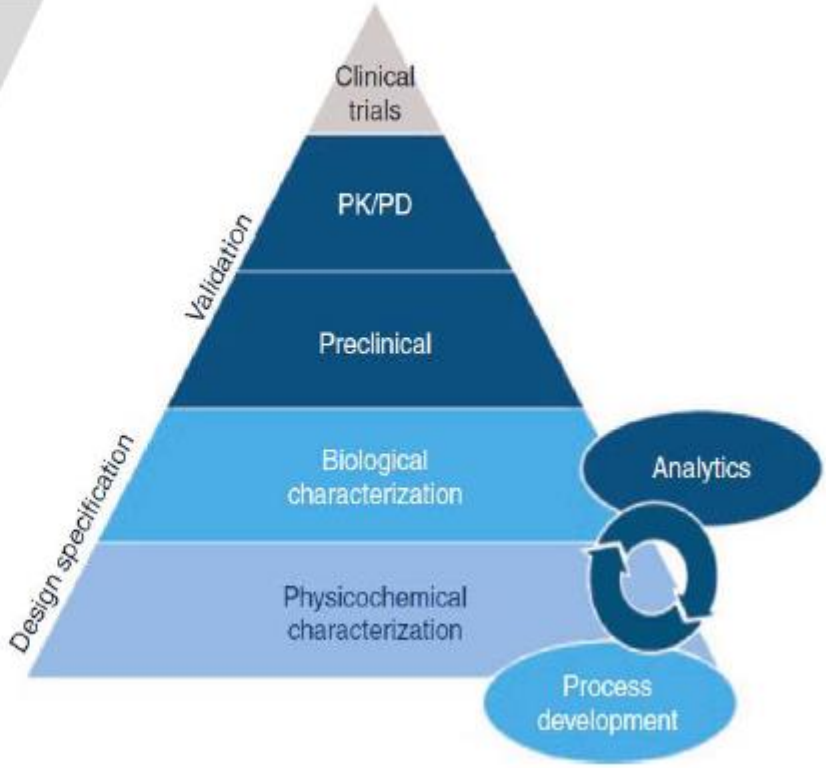
Biosimilar	Ab frequency	Reference	Ab frequency
Omnitrope (SC)	0/51 (0.0%)	Genotropin	1/44 (2.3%)
Valtropin (SC)	3/98 (3.4%)	Humatrope	1/49 (2.0%)
Binocrit (IV)	2/314 (0.6%)	Erypo	3/164 (1.8%)
Silapo (IV) Silapo (SC)	0/305 (0.0%) 0/323 (0.0%)	Erypo Erypo	0/304 (0.0%) 0/230 (0.0%)
Ratiograstim (SC)	7/356 (2.0%)	Neupogen	2/134 (1.5%)
Zarzio (IV / SC) (Phase 1, crossover)	0%	Neupogen	0%
Nivestim	3/183 (1.6%)	Neupogen	0/95 (0.0%)
Bemfola	0/249 (0%)	Gonal-f	0/123 (0%)
Insulin Marvel §	T1DM: 25/114 (21.9%) T2DM: 14/131 (10.7%)	Humulin	T1DM: 16/114 (14.0%) T2DM: 17/136 (12.5%)
Remsima - AS - RA	37.5% 55.6%	Remicade	36.1% 54.3%

Data from EPARs at *www.ema.europa.eu*

§ Application withdrawn. Table courtesy of Martina Weise

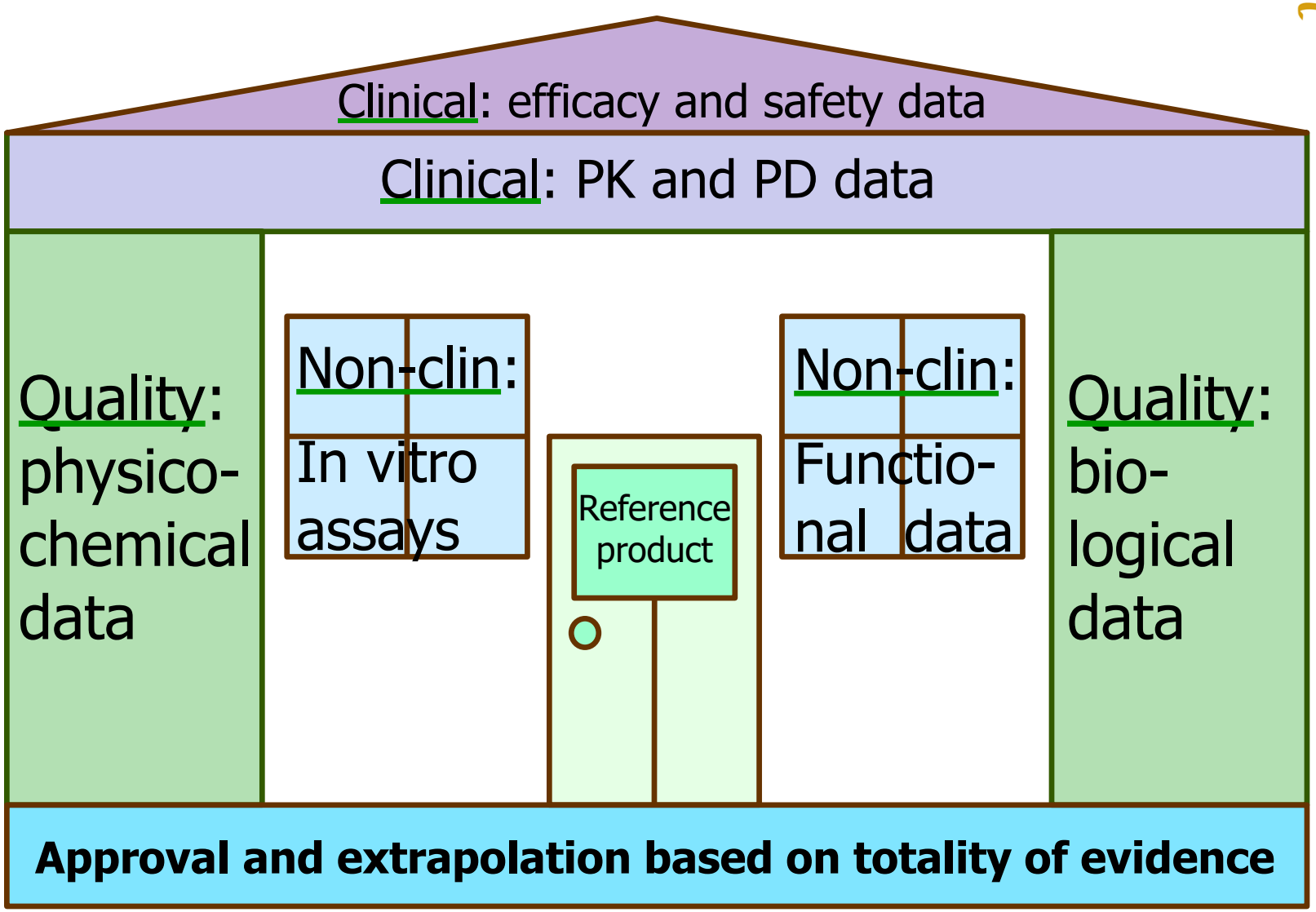
Biosimilars – the inverted triangle





From Elena Wolff-Holz,
EMA assessors training on biosimilars, Nov. 2016

The house of biosimilars



Development of biosimilars

Step-wise approach with comparability exercise at the level of

Quality

- Demonstration of a consistent manu-facturing process
- Plus biosimilarity in physicochemical and biological properties

Quality and non-clinical data as key first steps should show stringent biosimilarity

Non-clinic

- Demonstration of biosimilarity in functional in vitro tests
- In vivo comparison only in exceptional cases required

Clinic

- Extent of clinical studies may differ according to the biosimilar product

General considerations

What changed in general aspects of biosimilar development?

- **Definition of biosimilar product**
  - Acceptance of the term „new version" of the active substance
  - Does not refer to the drug product which is always to be seen as individual
- **Use of the reference product**
  - **Non-EEA reference product** may be used for (certain) clinical and in vivo non-clinical studies (since late 2014/early 2015)
  - Bridging data for showing representativeness to EU-licensed product (structural and functional, +/- pharmacology data)
  - 3-arm study or 2 separate studies with interstudy comparison

Quality aspects

What changed in quality aspects of biosimilar development?

- **Use of different expression systems**
  - Additional risk and concern, but in principle compatible with biosimilar approach
  - Consequences for comparability conclusion – (non)clinical studies to complement the program?
- **Quality target product profile (QTPP)**
  - **Statistical approach** for comparability ranges of quality attributes ⇨ can we draw inferences on structural/functional characteristics?
  - Manufacturing changes of the reference may lead to shifts in QTPP with new ranges separate (consider range before – after)
- **Own life-cycle** of the biosimilar after approval

Non-clinical aspects

What changed in non-clinical requirements of biosimilar development?

- **Step-wise and risk-based approach** in non-clinical part
  1. Comparative in vitro studies (greatest importance!!)
  2. Determination of the need for in vivo studies (upon level of concern)
  3. In vivo studies (if at all then under **3Rs** = replace, reduce, refine)
     - Only in rare situations, e.g. use of novel excipients or expression systems
  - **No studies in non-relevant species** or without a relevant model
- **Immunogenicity**
  - Although animals are generally not predictive for immunogenicity in humans, its assessment may sometimes be needed to interprete the results of in vivo animal studies (PK/PD) ⇨ **banking of samples**

Clinical aspects

What changed in clinical requirements for biosimilars?

- **Need for clinical studies**
  - Depends on the level of evidence obtained in previous steps (quality and non-clinical data)
  - Clinical comparability exercise normally starts with PK studies +/- PD (establish similar exposure and functional responses in the body)
  - Followed by clinical efficacy and safety trial(s)
  - In certain cases, confirmatory PK/PD studies may suffice
- **Choice of the clinical model**
  - Can the comparability exercise be done in an unapproved indication? – in principle **yes**
  - Will this lead to licensing of the biosimilar in an additional indication? – presumably **no**

Clinical aspects

What about equivalence – non-inferiority – superiority?

- **Improved efficacy not acceptable**
  - Concept of „biobetters" not defined in EU regulation
  - In general requirement to show **equivalence** in efficacy
  - Non-inferiority designs to be discussed in scientific advice
- **Improved safety potentially supported**
  - **Less immunogenicity** compatible with biosimilar approach
  - If fewer neutralising antibodies ⇨ could artificially increase efficacy?
    ⇨ subgroup analysis in antibody-negative population
    ⇨ confirms similarity if it's not impacted by the immune response
  - Requirements for immunogenicity – pre- and post-licensing, duration of follow-up (6 – 12 months)

Aspects on extrapolation

- Extrapolation is the **most important** (and most contentious) **principle for biosimilars**
- Extrapolation as a concept is not new
  - Applied for generics, biosimilars, paediatric indications, other populations
  - Changes of manufacturing process for biological medicines
- Change in manufacturing leads to a **new version of the active substance**
  - This corresponds to the definition of a biosimilar
  - Typically, clinical data not required to substantiate manufacturing changes
- Extrapolation should be done in the light of the **totality of data**
- Implemented in all biosimilar products approved until now

Aspects on extrapolation

- The **mechanism of action** is key to extrapolation
  - Suitable assays more sensitively characterise the MoA than clinical study
  - If the same mechanisms of action (active site) or the same receptors are involved (e.g. erythropoetin, filgrastim) ⇨ extrapolation straightforward
  - Additional non-clinical **or** clinical data (e.g. functional assays, PK or PD parameters and/or efficacy/safety data) may have to be **generated if**
    - Different active sites or different receptors are involved which may have a specific impact in different therapeutic indications
    - Studied therapeutic indication is not relevant for the others in terms of efficacy or safety (e.g. extrapolation from RA to oncology indications)
    - Different safety profile in different therapeutic indications
- **Immunogenicity** is always an issue
  - Must be addressed ⇨ discussed on the basis of an integrated analysis

Relevant clinical factors

PK comparison – primary endpoints

- For generics we are mainly interested in comparison of the absorption of the test and reference
  - Usually measure AUC_{0-t} and C_{max}
- For biosimilars the exposure shows greater dependence on the **elimination phase**
  - Therefore, especially in case of i.v. administration C_{max} has less importance (⇨ secondary endpoint)
    - Focus is on AUC_{0-inf}
  - For s.c. administration both absorption and elimination are relevant
    - Measure both AUC_{0-inf} and C_{max} as primary endpoints
  - In addition C_{min} or C_{trough} as important secondary parameter

Relevant clinical factors

PK comparison – variability

- Needs to be taken into account for the PK study design
  - Impact on sample size
  - **Cross-over design** may reduce/eliminate the impact of variability on the outcome of the comparison
  - Dose to be chosen in steep part of the dose/exposure curve

- Extent of variability may be difficult to anticipate (due to scarce PK data of the originator product)

Relevant clinical factors

PK comparison – study population

- In most instances one dedicated **single-dose PK/(PD) study** in healthy volunteers
  - May facilitate choice of a sensitive dose
  - May decrease the impact of variability in exposure (e.g. via target-mediated clearance)
  - For some molecules not acceptable due to toxicity (e.g. rituximab)
- When an additional efficacy trial is performed, limited **PK/PD sampling** in the patient population can „qualitatively" confirm the results from HVs
  - Assessment of PK after repeat administration

Relevant clinical factors

PD comparison

- Secondary endpoints in PK/PD trial
  - Normally not powered for statistical demonstration of similarity
  - Studies are usually powered for primary PK comparison
  - **Qualitative/supportive evidence** of similar effects between test and reference
  - Often rather unspecific parameters, not validated as specific endpoints
- Can PD parameters provide confirmative evidence of biosimilarity at the clinical level ?

Relevant clinical factors

Comparison of efficacy and safety

- Low sensitivity of the clinical trial for demonstration of biosimilarity needs to be strengthened by using:
  - Most homogeneous/sensitive population
  - Most sensitive dose
  - Most appropriate model and endpoint
  - Most sensitive time-point of primary endpoint assessment
  - Most accurate definition of the equivalence margin (based on both statistical and clinical grounds)

Evidence for "simple" biosimilars

- Examples of molecules where **comparative PD** data may be sufficient for showing equivalence in efficacy
  - Biosimilar insulin (euglycaemic clamp test),
  - Low molecular-weight heparins (anti-FXa, anti-FIIa),
  - G-CSF/filgrastim (absolute neutrophil count),
  - Interferons α and β (HCV viral load and MRI of MS lesions, resp.),
  - Teriparatide (PK data only !),
  - …. ?
- This requires a **primary validated PD surrogate endpoint**
  - PD endpoint then co-primary with PK endpoint(s)
  - Study to be powered accordingly ⇨ PD equivalence margin

Evidence for "complex" biosimilars

- Monoclonal antibodies or other **more complex, larger proteins**, which pose specific challenges to the quality characterization and exhibit more than one mode of action
- In these cases a **phase III efficacy study** is still required ⇨ demonstration of **equivalence** on clinical endpoint(s)
  - Serves to confirm comparable clinical performance of the biosimilar and the reference product
  - Provides the clinical basis for extrapolation to other indications
  - Is only one piece of the puzzle for interpretation of the totality of data

Evidence for "complex" biosimilars

Infliximab: extrapolation – rheumatology to IBD

- 2 different receptors/ligands on immune cells involved: ⇨ **sTNFa** (major part of activity, modulated via Fab fragment) and **mTNFa** (additional MoA – ADCC & CDC – modulated via Fc part)
  - Lower percentage of afucosylated glycoforms with lower binding to FcγRIIIa/b ⇨ 20% lower ADCC in most sensitive test system (Jurkat as target cells and NK as effector cells)
  - No differences in ADCC with serum/whole blood/PBMCs as target cells
  - Functional tests including transmembrane binding, reverse signalling and apoptosis were comparable
- Based on **totality of evidence** the CHMP concluded that the observed difference in afucosylated species is not clinically relevant and agreed to extrapolate with approval of all indications

Evidence for "complex" biosimilars

Rituximab: extrapolation – rheumatology to oncology

- Interaction with same receptor (binding to transmembrane CD20) results in **different cell-specific effects** (different mechanism of B-cell depletion) ⇨ can we extrapolate to different indications?
  - Non-clinical and clinical studies, investigating depletion of CD20-positive cells by ADCC/CDC/apoptosis and PK/PD, respectively
  - Phase III study in RA is acceptable, sensitive population, no cytotoxic co-medication, less variability in amount of tumour burden and consequently target-mediated clearance
  - Clinical bridging, e.g. via additional (smaller) PK ± efficacy study in patients with oncologic disease like AFL or DLBCL
- **Totality of evidence** may allow extrapolation in both directions

Evidence for "orphan" biosimilars

- **Examples**
  - Products for treatment of cystic fibrosis, paroxysmal nocturnal hemoglobinuria and atypic hemolytic uremic syndrome
- **Feasibility challenges**
  - The number of patients precludes a statistical definition of "hard" equivalence margins
  - This also impedes an adequate safety database pre-licensing
  - PD surrogate endpoints have great importance (but often not available and/or not validated)
  - Can PK comparison alone be sufficiently reassuring?
  - Additional challenges for extrapolation to other indications
- Weight of evidence rests with **quality** (physicochemical and biological) **and** pre-clinical/**functional** in vitro comparison

Evidence for "locally acting" biosimilars

- **Examples**
  - Products for treatment of cystic fibrosis, age-related macular degeneration and other diseases of the eye
- **Specific problems**
  - PK comparison largely infeasible due to very low systemic levels
  - This also affects the generation of safety data pre-licensing ⇨ systemic exposure most likely too low to make a comparative assessment
  - Comparison of local safety is crucial ⇨ apart from the active substance attention must be payed to impurities and excipients
  - PD endpoints may play a more prominent role to compensate for missing PK data

What have we learned, what are the future challenges?

- Extrapolation has until now proven to be successful
- Use of a non-EEA reference product is allowed under certain pre-requisites
- Animal data are very rarely needed
- Assessment of biosimilarity in quality attributes should be strengthened – new approaches under discussion
- Tailoring of clinical evidence is important
- Feasibility aspects for specific products must be considered
- Collection of post-marketing safety / immunogenicity data should be defined more precisely
- Education and communication to health care community and patients is key and needs to be improved

Thank you for your interest and time