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EMA Scientific Advice & Biosimilar PK trials

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Introduction

- What EMA Scientific Advice is and is not
- What forms do exist
- Who decides?

- The brief “what“ and “why“ of biosimilars
- Current status (Marketing authorisations)
- How the PK of Biosimilars is studied
- Wrap up and discussion

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European Scientific Advice – an introduction

European Scientific Advice

Aligning of a Drug Development with regulatory authorities

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- Process hosted by EMA
- Assessed by national experts in Member States
- Discussed in Scientific Advice Working Party at EMA
- Signed by CHMP

Scope and Application

Apply at EMA and ask about studies/experiments

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- Apply and inform yourself @ https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance

- After Submission comes the validation
  - Are your questions scientific?
  - Regulatory questions not discussed.
  - No preliminary data assessment

Key question on quality/preclinical/clinical (statistical) level:

Is your model/test/study sensitive to support assessment of the drug's benefit risk?

Forms of Scientific Advice

Choose the model that suits your cause

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- Standard
- Protocol Assistance (for orphan drugs)
- Qualification Advice (not about drug development, but tests, endpoints etc.)
- HTA parallel advice (if you also have health economic questions)
- Parallel with FDA
- Biosimilar Pilot

The Scientific Advice Working Party

Who they are, what they do

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- 36 members
  - 3 members: Committee for Orphan Medicinal Products
  - 3 members of the Paediatric Committee,
  - 3 members of the Committee for Advanced Therapies
  - 1 member of the Pharmacovigilance Risk Assessment Committee
- Not nominated by country
- Meet 11 times a year
- Members receive list with applications and apply
  - By expertise and ressources
- Two members are assigned

The First Report

When the actual work happens

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- Both teams work independently
- First reports submitted
- Both coordinators present the Scientific Advice to the Working Party
  - Is the request clear?
  - Are positions divergent?
  - Is a Discussion Meeting with the company needed?

- **Two ways possible …**

The „easy“ route

When everything seems clear…

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- Similar positions
- Joint Report (controlled by a Peer Reviewer)
- Adopted by CHMP
- Final Letter
- End of Procedure

When it is not so easy …

Company proposals incomplete or unclear

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- Further questions to the company
- List of Issues
- Company invited to next meeting
- Issues are clarified in a discussion
- Joint Report and adoption are written after the Discussion Meeting

Clarification Request

When the Comanies have questions on the final letter

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- Clarification is possible
- Only on already discussed issues
- No new proposals
- Those should be submitted as a Follow Up

The worth of a Scientific Advice letter

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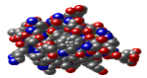
- Part of dossier for Marketing Authorisation
- Legally not binding
- Compliance to EMA scientific advice is part of assessment
- Recommendations not binding for Regulatory Authorities

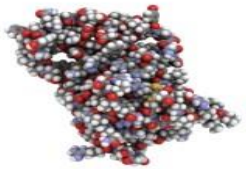
Biosimilar PK studies

Biologicals are complex

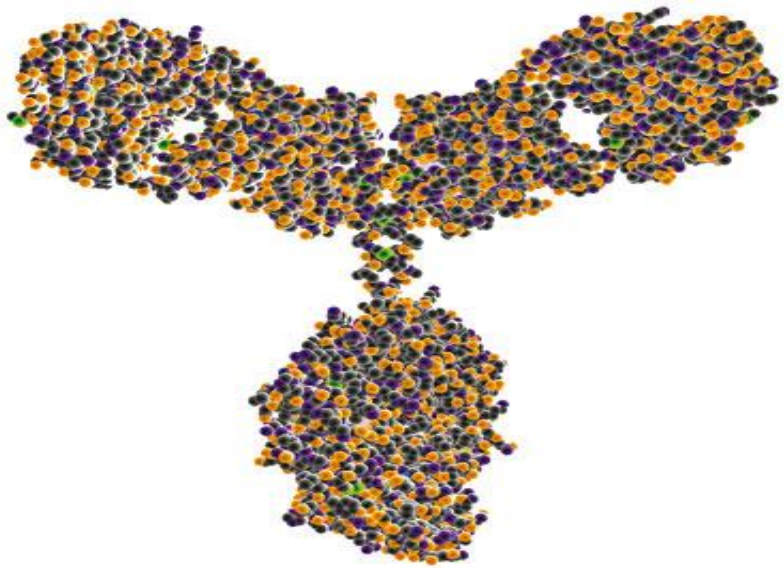
Aspirin
180 Daltons



Insulin
5 700 Daltons



Growth hormone
22 000 Daltons



Monoclonal antibody
150 000 Daltons

www.laborjournal.de, www.123rf.com, www.wikipedia.org

Definitions

Novel Biologics:

- New mechanism of action
- New targets
- New technology (host cells, processes…) compared to existing biologics.

Most important cornerstones

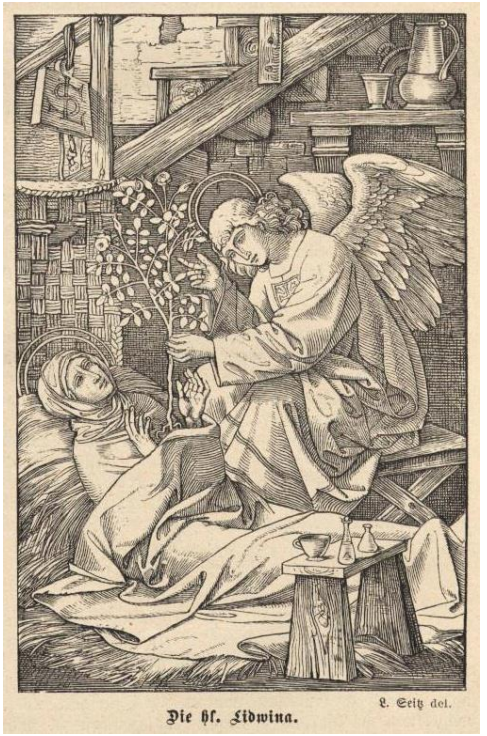
Biosimilars have:

- Same B/R profile as “originator” MP
- same indications.
- Marketing Authorisation via “comparability exercise” to originator
- Via a stepwise approach (Quality,Preclinical,PK,Clinical)

To illustrate…

Examples for treatment costs

Tysabri® (natalizumab)	one pack N1	€ 2428.06 (yearly € 29136.72)
Soliris® (eculizumab)	one pack N1	€ 5827,19 (yearly up to € 600.000)
Ocrevus ® (ocrelizumab)	yearly cost	€ ~33000



Biosimilars contribute to keep/make innovative drugs available to a wide range of patients!

Disclaimer: Pricing is not taken into account by regulators

Source: wikipedia, medizinfuchs.de October 2018

Centralized Marketing Authorisations

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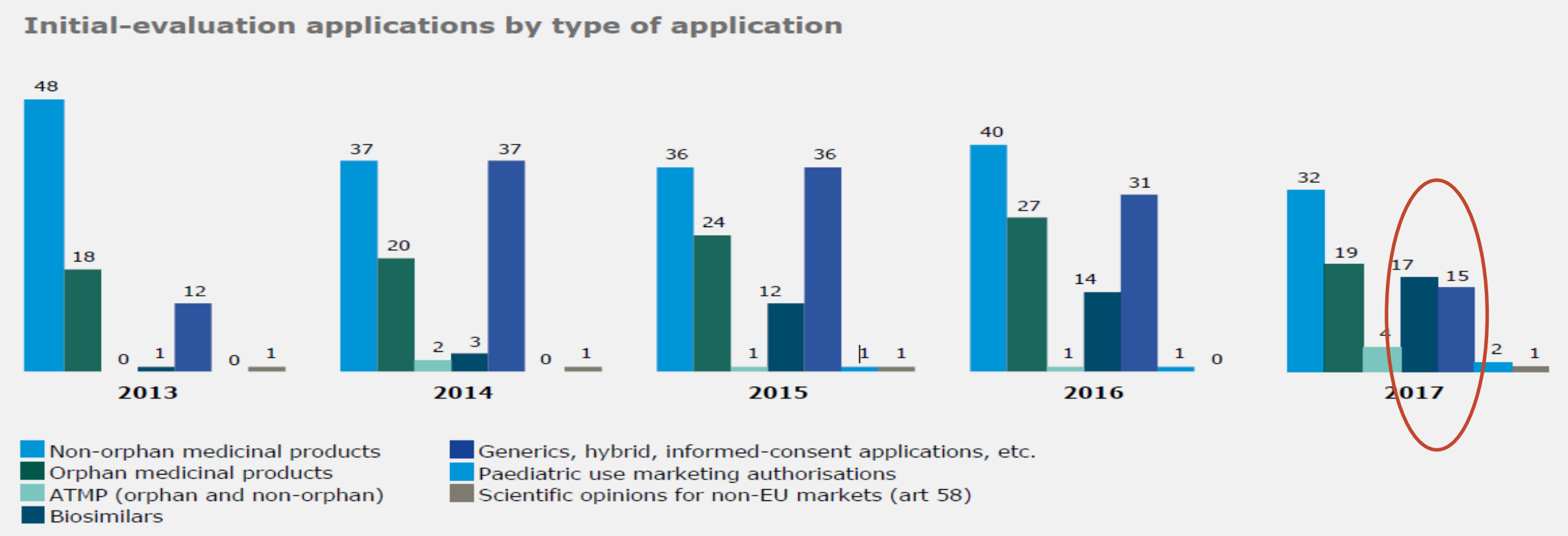
Biosimilar Applications steadily increase…



Quelle: EMA Annual Reports

Biosimilar Development Program (EU)

A stepwise approach to comparability

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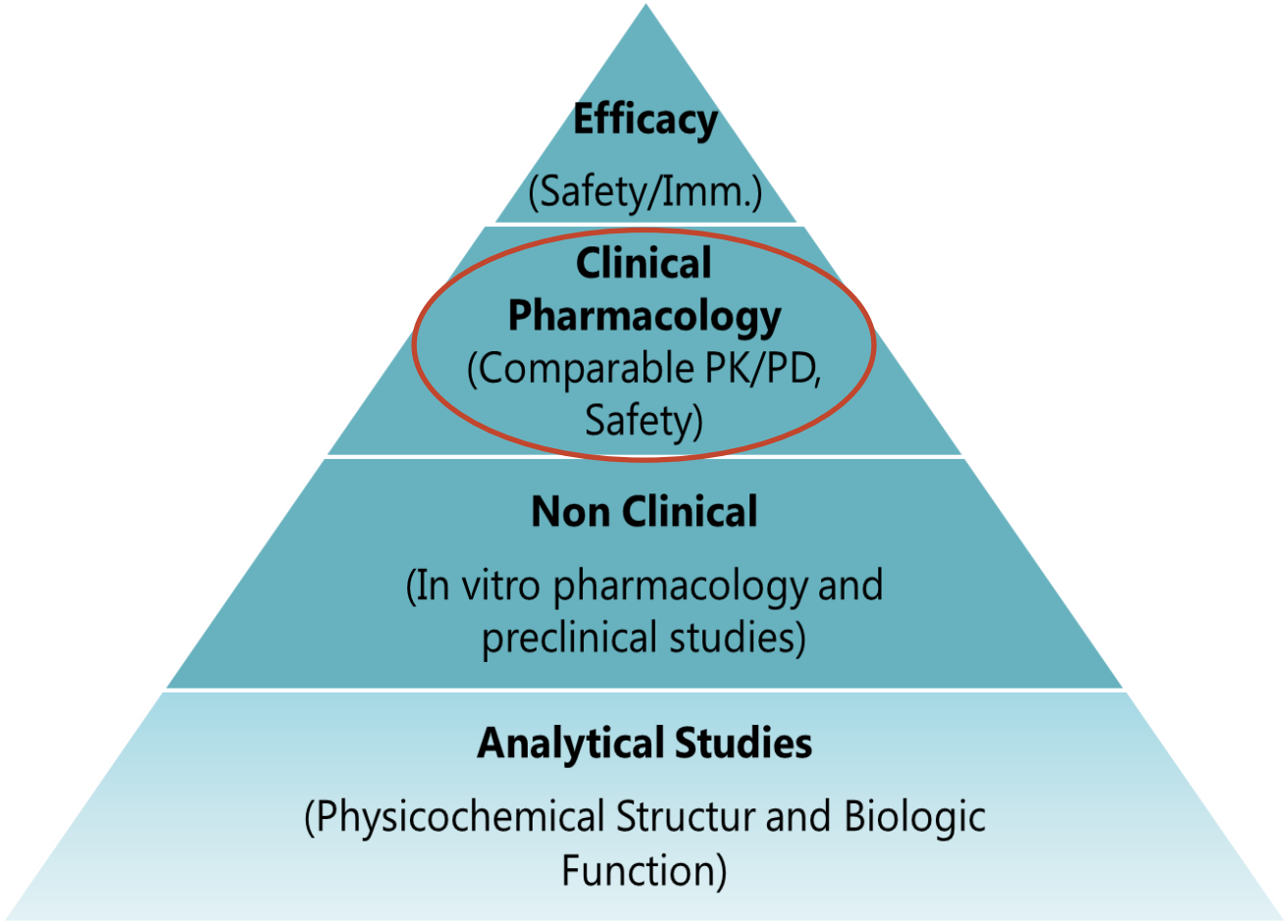

Ressources

- All Biosim Guidelines: *http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp*

- Three “Stages“
  - User guidance “Overarching“
  - Non Clinical/Clinical and Quality
  - Product specific

  e.g. „monoclonal antibodies“ EPO, LMWH, Insulin, GCSF, FSH, Growth hormone;

Biosimilar PK studies

- Equivalence design
- Parallel vs Crossover
- Dose and Population sensitive
- Should include immunogenicity assessment
- Non EEA sourced RMP can be used (e.g. ICH countries)

PK trial in Efficacy trial

Applicant may also provide PK subsets

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- Not strictly mandatory
- No confirmative equivalence testing
- Usually descriptive comparisons of Trough levels
- Only performed in a subset
- Can provide insight regarding immunogenicity

No PK data at all?

In some cases that‘s ok!

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- Active substance is not reliably measurable (e.g. enoxaparin)
- AND direct functional correlates are available
- Very rare scenario

Challenges in Biosimilar PK studies

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When there are unpleasant surprises …

- How to deal with a failed PK trial
  - Reason?
  - Show stopper?
  - Second trial?
  - Weight of trials?

- When the PK of the originator is not sufficiently understood
  - When it‘s known: How to plan a study?
  - When it‘s unknown: How to address a failed study (see above)
  - Recent case: pegylated filgrastims (oversensitive PK? Unexpected variability?)

PK/PD Studies in Biosimilar Development

- PD markers added to the pharmacokinetic studies whenever feasible.
- Comparative PK/PD studies may be sufficient to demonstrate clinical comparability of the biosimilar and the reference medicinal product

Hypothetical Example PK/PD Natalizumab

- Healthy volunteers possible (more sensitive, but: reduce risk of leucencephalopathy, e.g. uninfected with JC virus)

- mAB → long half life (9-10 days) → parallel design

- Primary endpoint: AUC (0-inf)
- Challenge: lack of meaningful PD marker
  - α4-integrin receptor saturation (AUEC?), (lymphocyte subset analysis, sVCAM-1 concentration measurements…)

→Comparable Efficacy and Safety to be confirmed in Clinical trial

Hypothetical example teriparatide

The smallest of the small biologics, close to generic

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- Reminds of a generic study
- Short half life → cross over design
- Not toxic → male healthy volunteers
- S.c. administration: primary endpoint → AUC (0-inf) and C(max)
- → simple molecule to compare on quality and functional level, low immunogenicity, no efficacy trial mandatory

Summary Scientific Advice

Stay on the path for Marketing Authorisation

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- Hosted by EMA
- Performed by National Experts
- Different Forms, for different purposes
- Discusses Models and Studies NOT data
- Important cornerstone for MA but not binding

Summary – Biosimilar Development

- EMA regulatory framework with high standards
- Main goal: make differences to the originator visible
- Most comparability work (functional and structural) performed on quality level
- PK is most sensitive clinical model
- The best suited PK design strongly depends on the molecule (see product specific guidelines)

Thank you!

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DESIGNVORGABE

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Bitte immer Unterüberschriften verwenden

- **„Non-identicality“ is a normal principle in biotechnology.**
- No batch of any biological is „identical“ to the others
- The „art“ is to demonstrate that the biosimilar is as close as possible to its reference product in all relevant functional and structural aspects, within current technical and scientific limitations
  (inherent variability)

Per definition

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European Medicines Agency

London, 22 October 2008
Doc. Ref. EMEA/74562/2006 Rev. 1

Questions and Answers on biosimilar medicines (similar biological medicinal products)

"A biosimilar medicine is a medicine which is similar to a biological medicine that has already been authorised (the 'biological reference medicine'). The active substance of a biosimilar medicine is similar to the one of the biological reference medicine. Biosimilar and biological reference medicines are used in general at the same dose to treat the same disease. ***Since biosimilar and biological reference medicines are similar but not identical****, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional."*

http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf

- A biosimilar development programme is ”scientifically tailored” towards a different objective rather than ”abridged”.
- It establishes benefit and risk via the biosimilar comparability exercise in the most sensitive models
- It is not the number of patients studied that counts; it is the strength of evidence provided.
- Biosimilar review is strict and ensures marketing authorisation only of top quality biosimilars in the EU.
- Only upon approval a biosimilar candidate becomes a ”true biosimilar”

EMA/FDA: agreement

EMA

- **complexity** of molecules and production process
- **step-wise** approach
- evidence from **complete data package** (Q/S/E) possible extrapolation
- equivalence designs (required)
- **post-marketing** commitments in the RMP, immunogenicity pre + post-approval

FDA

complexity of molecules and production process

step-wise approach

totality of evidence(CMC/non-clinical/clinical),possible extrapolation

equivalence designs (preferred)

post-marketing safety monitoring, immunogenicity pre + post-approval

- Ocrelizumab anti cd 20 roche 2018 primary progredient und rr MS (33000 vs 3000 Euro) Mab thera indikation n ein, aber anscheinend viel off label useNon-Hodgkin’s lymphoma (NHL)
- MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell
- Chronic lymphocytic leukaemia (CLL)
- Rheumatoid arthritis
- Granulomatosis with polyangiitis and microscopic polyangiitis

- Glatiramer Acetate
- Non biologic complex drugs, synthetically produced therefore no biologic, hence not part of biosimilar framewort
- Complexity of manufacturing process however calls for higher standards for follow on product than for generics
- Status quo: are handled on individual case decisions.
- Requirements are mostly „borrowed“ from biosimilar guidelines
- Complex mix of polypeptides, active substance not known