A Clinician´s Guide to Biosimilars in Oncology:
Understanding the Science of
Extrapolation and Interchangeability

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Biosimilar Medicinal Products
Working Party (BMWP)

Paul Ehrlich Institut
Federal Agency for Vaccines and Biomedicines

The views presented here are my own and do not necessarily reflect the views of the Paul-Ehrlich-Institut.
Dr Elena Wolff-Holz
Disclosures September 2017

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  - Paul Ehrlich Institute, German National Health Service

- Honoraria received:
  - NONE
Understanding the Science of Extrapolation and Interchangeability

- Nomenclature
- Regulatory framework in EU
- The science of developing biosimilars
- The science of extrapolation
- Interchangeability
- Closing remarks
Understanding the Science of Extrapolation and Interchangeability

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  - Regulatory framework in EU
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  - Closing remarks
Importance of nomenclature...
Understanding the Science of Extrapolation and Interchangeability

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- Closing remarks
Definition of a Biosimilar exists in Europe since 2001

…………. it´s a LAW

Directive 2001/83/EC (as amended)

Article 10: „Generics“ and legal basis for „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. ”
Regulation of Biosimilars in the EU

Legislation
- Directive 2001/83/EC
- Directive 2004/27/EC*

Guidance
- Overarching guideline
- Quality guideline
- Non-clinical/Clinical guideline
- Revised Overarching guideline
- Revised Quality guideline
- Revised Non-clinical/Clinical guideline

Product-class specific guidelines
- somatropin
- epoetin
- filgrastim
- infliximab & follitropin
- insulin glargine
- Etanercept
- Enoxaparin
- Teriparatide
- Rituximab

Product Authorisations

*amending Directive 2001/83/EC
Biosimilar Product Review (August 2017)*

66 MAAs submitted

53 MAAs post-review

13 MAAs under review

2 Negative

Interferon alfa
Insulin

12 Withdrawn (pre-approval)

Insulin (6)
Epoetin (1)
Pegfilgrastim (4)
Trastuzumab (1)

3 Withdrawn (post-approval)

Filgrastim (2)
Somatropin (1)

39 Positive opinions

36 Valid MAs

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Infliximab (3)
Follitropin alfa (2)
Etanercept (2)

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Filgrastim (7)
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Follitropin alfa (2)
Etanercept (2)

13 MAAs under review

Adalimumab (3)
Bevacizumab (2)
Infliximab (1)
Insulin glargine (1)
Pegfilgrastim (2)
Trastuzumab (4)

* Information on EMA website
**Biosimilars in the EU (06. Sep 2017; EMA website)**

22 distinct Biosimilars (= 36 products) exist for 11 different Reference products.

<table>
<thead>
<tr>
<th>Medicine Name</th>
<th>Active Substance</th>
<th>MAH</th>
<th>Status</th>
<th>Authorisation</th>
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</tr>
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<td>瑞hatan</td>
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<td>Sandoz</td>
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<td>BioPartners</td>
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Understanding the Science of Extrapolation and Interchangeability

- Nomenclature
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- Closing remarks
Changes in the manufacturing process of biologicals occur frequently

→ Concept is not new!

• Any change of the manufacturing process of the originator leads to a new version of the active substance

• The manufacturer has to demonstrate the comparability of new versions from the old and the new manufacturing process

ICH guideline Q5E
Comparability Exercise for different (similar) versions of the same active substance

Quality
- impurities
- batch inconsistency
- contaminants
- aggregates
- microheterogeneity
- fragments

Non-Clinical
- tissue cross-reactivity
  - binding—Fab/ Fc
  - potency
  - toxicity
  - immunotoxicity

BRIDGING
- Primary structure
- Protein content
- Higher order structure
- High molecular weight species
- Charge
- Glycosylation profile

Clinical
- PK/PD
- efficacy data
- safety data
- immunogenicity data
Manufacturing changes authorized by EMA
(EPARs of 29 Mabs: Total manufacturing changes = 404)

- Change filter supplier
- Move equipment within same facility
- Move to new production facility (same manufacturer)
- Change cell culture media
- New cell line or major formulation change

<table>
<thead>
<tr>
<th>Nature of Process Change</th>
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<th>Move equipment within same facility</th>
<th>Move to new production facility (same manufacturer)</th>
<th>Change cell culture media</th>
<th>New cell line or major formulation change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Level / Data Requirements</td>
<td>Low Risk</td>
<td>Analytical data</td>
<td>Process data</td>
<td>Moderate Risk</td>
<td>Analytical data</td>
</tr>
</tbody>
</table>

- New manufacturer of active substance (AS)
- Change of in process tests with widening of limits
- Change purification process of active substance (AS)
- Manufacturing change known to impact mechanism of action

Manufacturing of biologics has inherent variability

Need to
- define measurable product quality attributes
- Set specifications
- define proven acceptable ranges
New version of the active substance implies
….similar (!) and not identical

Rituximab with expiry dates from Sep 2007 to Oct 2011
Using cation exchange chromatography (a), % basic variants (b), ADCC (c) and glycan mapping (d)
Manufacturing changes authorized by EMA

(EPARs of 29 mabs: Total manufacturing changes = 404):

Figure 2. Number of manufacturing changes for monoclonal antibodies in their European Public Assessment Reports according to risk category (during the search period all non-proprietary names relate only to the trade named medicines listed in Table 1).

Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents.

Changes in the manufacturing process of biologicals occur frequently

► Typically, clinical data is not required to substantiate manufacturing change.

► But if at all, then one clinical trial in one therapeutic indication with extrapolation to all therapeutic indications is sufficient

(so far required only once: Aranesp Phase 3)

► BWP/CHMP have experience in judging impact of differences in quality attributes.
Summary: Changes in the manufacturing process of biologicals occur frequently

Concept is not new!

Definition of a Biosimilar (Overarching Guideline CHMP/437/04 Rev. 1):

“A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product.”
Example: Establishing Biosimilarity with Comparability studies  Truxima versus MabThera –

Comparative studies

- Analytical: physical and chemical properties
- Functional: biological/pharmacological activity
Comparability studies  Truxima versus MabThera – Overview of comparative quality studies

<table>
<thead>
<tr>
<th>Molecular parameter</th>
<th>Methods for control and characterisation</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary structure</td>
<td>Amino acid analysis</td>
<td>Identical primary structure</td>
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<tr>
<td></td>
<td>Molar absorptivity</td>
<td>Intact mass comparable</td>
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<tr>
<td></td>
<td>N-terminal sequencing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-terminal sequencing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peptide mapping by HPLC</td>
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<tr>
<td></td>
<td>Determination of intact mass</td>
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<tr>
<td>Secondary and higher order structure</td>
<td>Fourier Transform Infra-Red spectroscopy</td>
<td>Highly similar secondary and higher order structure.</td>
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<tr>
<td></td>
<td>Circular Dichroism</td>
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<tr>
<td></td>
<td>Differential Scanning</td>
<td></td>
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<tr>
<td></td>
<td>Calorimetry</td>
<td></td>
</tr>
</tbody>
</table>

- Similar post-translational modifications included deamidation, oxidation and C-terminal lysine variants,
- Highly similar number and distribution of charged variants
- highly similar glycosylation profiles,
- highly similar monosaccharide (Fucose, N-acetyglucosamine, Galactose and Mannose) sugar contents
- Highly similar sialic acid (N-acetylneuraminic acid (NANA) contents
- similar levels of residual process-related impurities (such as host cell protein, Host Cell DNA and rProtein A) were shown.
Mechanism of rituximab-mediated cell death

Direct apoptosis induction in vitro is mainly seen in rapidly dividing Burkitt lymphoma cells but is very hard to demonstrate in some other lymphoma cell types.

FcR polymorphism(s) have impact on in vivo response in Follicular lymphoma (FL) suggesting that ADCC is more important in FL but less important in CLL.

CD20 levels on the B cell surface, and B cell count differ largely between NHL and Rheumatoid Arthritis (RA) patients due to the range of tumour burden among patients.
### Comparability studies  Truxima versus MabThera – Overview of comparative preclinical studies

<table>
<thead>
<tr>
<th>Molecular parameter</th>
<th>Methods for control and characterisation</th>
<th>Key findings</th>
</tr>
</thead>
</table>
| Binding assays and *in vitro* bioassays | **Binding affinity to CD20**  
**C1q binding affinity**  
**Fcγ receptors**  
(FcγRIIIa-V, FcγRIIIa-F, FcγRIIIB, FcγRIIa, FcγRIIb and FcγRI) **binding affinity**  
and  
**FcRn binding affinity**  
**CDC**  
**ADCC**  
**Apoptosis** bei FACS analysis | **Highly similar binding affinity to CD20**  
(the primary mechanism of action of rituximab)  
**A similar correlation between glycosylation and Fc function of Truxima and MabThera/Rituxan was shown**  
**Highly similar biological activities in assays representative of the known and putative mechanisms of action of Rituximab.** |
Implication 1: Paradigm Shift

“Totality of evidence“

→ Several criteria for similarity will determine “biosimilarity”
→ Sensitive attributes are evaluated with multiple complimentary methods

Paul-Ehrlich-Institut
Implication 2: Source of Information for Biosimilars is European Public Assessment Report (EPAR)

- CTD Module
  - 3. Quality
  - 4. Non-Clinical
  - 5. Clinical

- Originator
  - Cross reference

- Biosimilar
  - Cross reference
  - Integrated Comparability Exercise
    - product specific Quality, Safety and Efficacy

- SmPC
- EPAR
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Concept of Extrapolation is not new! 
→ It applies to ALL MEDICINES!!

Extrapolation is defined as

“….extending information and conclusions available from studies in one or more subgroups of the source patient population…

….to make inferences for another subgroup of the population … thus reducing the need to generate additional information... to reach conclusions for the target population ... “

Concept paper on extrapolation of efficacy and safety in medicine development. EMA, 2013—currently under revision
Concept of extrapolation is addressed in Overarching Guidelines of Biosimilars
EMEA/CHMP/BMWP/42832/2005 Rev. 1

Extrapolation:

- Requires scientific justification (not automatically granted)
- Is possible, IF overall data on biosimilarity allow for it
- „Totality of-evidence“
Considerations for extrapolation

Usually unproblematic when

- **same MoA/receptor** is involved and no indication specific safety concern exists
  - ➔ no reason to request additional data

- **same receptor** but different target-cell specific downstream signalling
  - ➔ no reason to request additional data
Considerations for extrapolation

Additional data is necessary, if

- Different active sites of the biologic agent or different target receptors

- Studied therapeutic indication is not relevant for the others in terms of efficacy or safety (e.g. extrapolation from R.A to oncology indications)

- Different safety profile in different therapeutic indications

→ e.g. functional assays and/or PD parameters and/or clinical data
Considerations for extrapolation

Additional data is necessary, if

- Different active sites of the biologic agent or different target receptors
- Studied therapeutic indication is not relevant for the others in terms of efficacy or safety (e.g. extrapolation from R.A to oncology indications)
- Different safety profile in different therapeutic indications

→ e.g. functional assays and/or PD parameters and/or clinical data
The scientific justifications for extrapolation of data to support a demonstration of biosimilarity in the indications for which the Applicant is seeking licensure include:

- The mechanism of action (MOA) of trastuzumab on human tumor cells that overexpress HER2 includes inhibition of proliferation and antibody-dependent cellular cytotoxicity (ADCC). This MOA is independent of the disease setting.

- Demonstration that MYL-1401O is highly similar to US-Herceptin based on extensive analytical characterization data

- Similar pharmacokinetics (PK) was demonstrated between MYL-1401O and US-Herceptin in healthy subjects. A similar PK profile would be expected between MYL-1401O and US-Herceptin across the other indications for use.

- In MYL-Her-3001, the frequency of anti-drug antibody formation was low and there were no notable differences between MYL-1401O and EU-Herceptin. A sufficient scientific bridge was established to justify the use of clinical data generated with EU-Herceptin to support a demonstration of biosimilarity of MYL-1401O to US-Herceptin. Accordingly, similar immunogenicity would be expected between MYL-1401O and US-Herceptin in other indications of use.

- Similar clinical safety and efficacy profile was demonstrated between MYL-1401O and EU-Herceptin in HER2 positive metastatic breast cancer patients. Accordingly, similar safety and efficacy would be expected between MYL-1401O and US-Herceptin. As analytical and PK similarity was demonstrated between MYL-1401O and US-Herceptin, a similar safety and efficacy profile would be expected in other indications for use.
FDA Panel Unanimously Backs Avastin and Herceptin Biosimilars

Posted 13 July 2017

The US Food and Drug Administration's (FDA) Oncologic Drugs Advisory Committee (ODAC) on Thursday unanimously backed the approval of biosimilar versions of two of Roche's top selling cancer drugs, Avastin (bevacizumab) and Herceptin (trastuzumab).

In the morning session, ODAC members voted 17-0 in favor of approving Amgen's Avastin biosimilar candidate, ABF 215, for six of Avastin's indications. However, the committee did not consider whether Amgen's data would support approval for two of Avastin's indications for ovarian cancer, as they are covered by orphan drug exclusivity until 2021 and 2023.

In the afternoon session, ODAC members voted 16-0 in favor of approving Mylan's Herceptin biosimilar candidate, MYL-1401O, for all of Herceptin's indications, including an indication for metastatic gastric cancer, which is protected by orphan drug exclusivity through 20 October 2017.

In both cases, ODAC and FDA reviewers found there were no clinically meaningful differences between the reference products and the biosimilars, though some panel members expressed concerns about extrapolating data from studies in a single disease to multiple indications.

But ODAC Chair Bruce Roth, a professor of medicine at the Washington University School of Medicine, reminded the panel that oncologists have to extrapolate data every day in the clinic.

"I think the magnitude of extrapolation is no greater here than we experience on a daily basis in the clinic," he said.
Summary: Extrapolation of Biosimilars

- Extrapolation is not a new concept and is based on sound scientific principles.
- In case of remaining doubt, additional binding, functional and/or clinical data are required.
- Regulators in the EU take a careful approach in order not to jeopardize the safety and wellbeing of patients.
- Explanation of the reasons for extrapolation granted by CHMP is presented in the EPAR.
- Much real life experience with extrapolation exists.
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**Definitions of interchangeability largely agreed within EU**

**Switching**
The decision by the treating physician to exchange one medicine with another medicine with the same therapeutic intent in a given patient.

**Interchangeability**
means the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient **on the initiative**, or **with** the agreement of the prescriber.

**Substitution**
practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level **without consulting the prescriber**.
There is no “substitutability determination” at EU level

**Automatic Substitution (EU)**
practice whereby a pharmacist **is obliged to dispense** one medicine instead of another equivalent and interchangeable medicine due to national or local requirements (**without consulting the prescriber**)
Definition in United States

Definition: Interchangeability

Interchangeable or Interchangeability means:
- the biological product is biosimilar to the reference product;
- it can be expected to produce the same clinical result as the reference product in any given patient; and
- for a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

Note: The interchangeable product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

Patient Protection and Affordable Care Act; Mar. 23, 2010.
Interchangeability: Theoretical considerations
Changes in the manufacturing process of biologicals are ongoing

... in real life:
Different versions of same active substance are de facto already being used interchangeably without necessity for clinical studies.
A ‘Global Reference’ Comparator for Biosimilar Development

Christopher J. Webster1, Gillian R. Woollerts2

Aims to establish a 'global reference' or 'reference product' for biosimilar development.

Abstract: Major drug regulators have indicated their willingness to accept some development data for biosimilars generated with reference product versions licensed in different jurisdictions, but most authorities require new bridging studies between these versions and the versions of the licensed product. The costs of these studies are not trivial and vary considerably, thus posing a significant challenge to the development of biosimilars.

Key Points:
- Bridging studies between an originator biological and biosimilar development benefit from scientific rigour.
- The authors propose conditions for the use of the originator as a basis for approval of the biosimilar.

Introduction: The need for a standardized approach to biosimilar development is highlighted, with a focus on the importance of bridging studies.

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10.1007/s40265-017-0224-4

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Understanding the Science of Extrapolation and Interchangeability

- Nomenclature
- Regulatory framework in EU
- The science of developing biosimilars
- The science of extrapolation
- Interchangeability
- Closing remarks
EMA Pharmacovigilance Project 2017: ongoing

Biological product identifiability in EudraVigilance (EV)

More than 49,000 cases received as spontaneous ADR reports from a reporter within the EEA between 01 Jan 2011 and 30 Jun 2016

Preliminary results show robust levels of overall product identification for classes of biologicals for which biosimilars are approved, in line with previous findings.

Product identifiability of selected suspected biologicals reported in spontaneous reports from European clinical practice

<table>
<thead>
<tr>
<th>Product</th>
<th>Total, n</th>
<th>Identifiable product, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>etanercept</td>
<td>19,716</td>
<td>19,012 96.4%</td>
</tr>
<tr>
<td>infliximab</td>
<td>12,045</td>
<td>11,342 94.2%</td>
</tr>
<tr>
<td>insulin glargine</td>
<td>2,446</td>
<td>2,394 96.6%</td>
</tr>
<tr>
<td>filgrastim</td>
<td>1,048</td>
<td>934 89.5%</td>
</tr>
<tr>
<td>epoetin alfa</td>
<td>1,084</td>
<td>1,045 96.4%</td>
</tr>
<tr>
<td>somatropin</td>
<td>1,047</td>
<td>1,006 96.1%</td>
</tr>
<tr>
<td>follitropin alfa</td>
<td>448</td>
<td>442 98.7%</td>
</tr>
</tbody>
</table>

95.5% overall
Batch number identification is generally poor
Identification using trade name is very good
Data from EudraVigilance database suggests continuous robust levels of product identification of biologicals from European clinical practice
These results are similar (or better) than previously published data on biosimilar identification in EV


We can be confident in our Pharmacovigilance system!
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Thanks for your attention!