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

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The views presented here are my own and do not necessarily reflect the views of the Paul-Ehrlich-Institut.

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## 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

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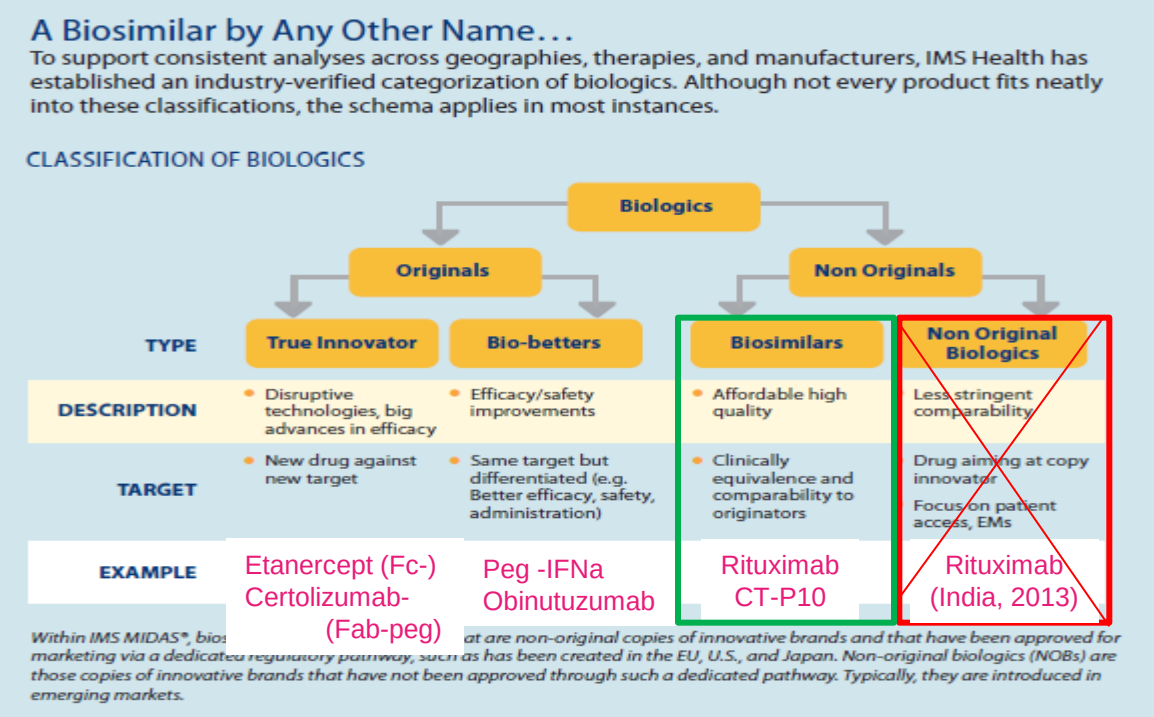
# Importance of nomenclature…



## A Biosimilar by Any Other Name…

To support consistent analyses across geographies, therapies, and manufacturers, IMS Health has established an industry-verified categorization of biologics. Although not every product fits neatly into these classifications, the schema applies in most instances.

CLASSIFICATION OF BIOLOGICS



*Within IMS MIDAS®, bios… at are non-original copies of innovative brands and that have been approved for marketing via a dedicated regulatory pathway, such as has been created in the EU, U.S., and Japan. Non-original biologics (NOBs) are those copies of innovative brands that have not been approved through such a dedicated pathway. Typically, they are introduced in emerging markets.*

Source: IMS HEALTH

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# Definition of a Biosimilar exists in Europe since 2001

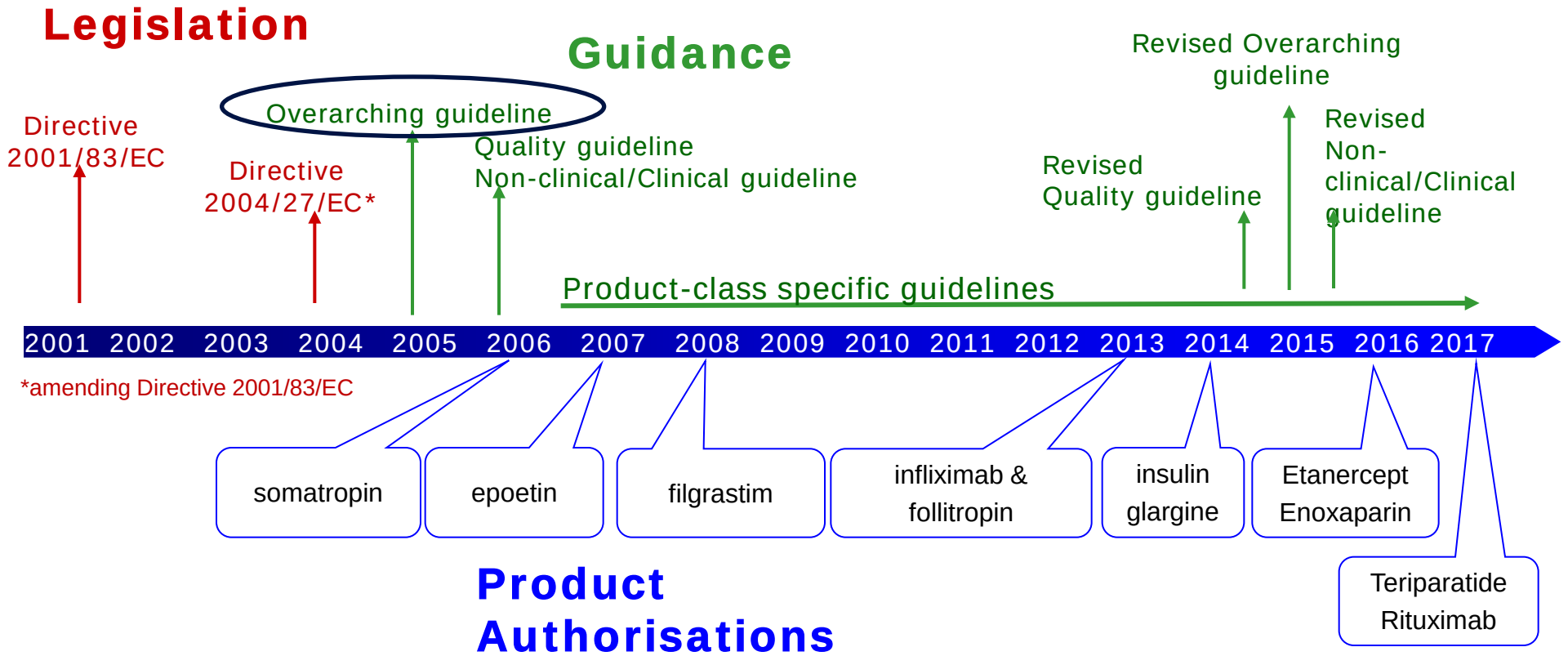
## ……. it´s a LAW

Directive 2001/83/EC (as amended)

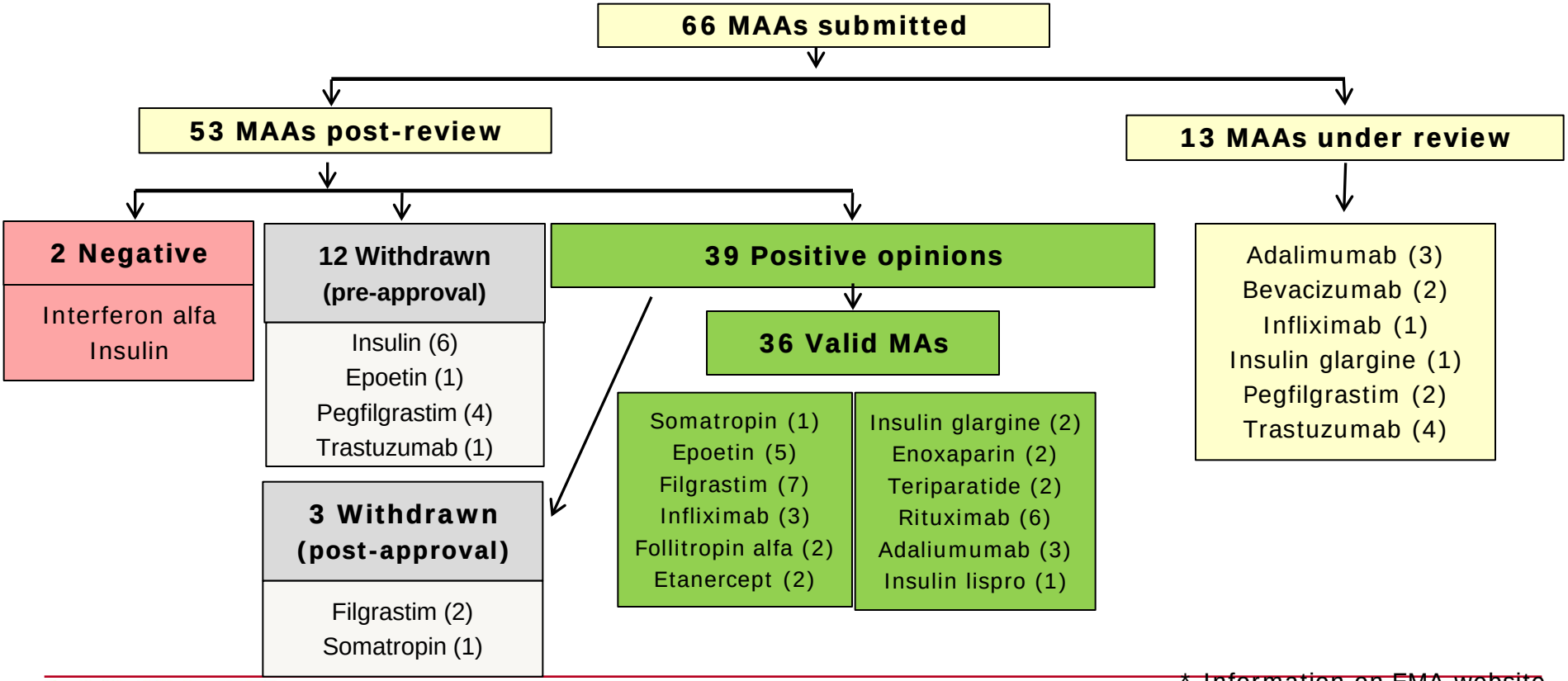
Article 10: „Generics“ and legal basis for „biosimilars“

- 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



# Biosimilar Product Review ( August 2017 ) *






* Information on EMA website

# Biosimilars in the EU ( 06. Sep 2017; EMA website)

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

| | Medicine Name | Active Substance | MAH | Status | Authorisation |
|---|---|---|---|---|---|
| 1 | Inhixa | enoxaparin | Techdow | Authorised | Sep 16 |
| | Thorinane | enoxaparin | Pharmathen | Authorised | Sep 16 |
| 2 | Abseamed | epoetin alfa | Medice | Authorised | Aug 07 |
| | Binocrit | epoetin alfa | Sandoz | Authorised | Aug 07 |
| | Epoetin Alfa Hexal | epoetin alfa | Hexal AG | Authorised | Aug 07 |
| | Retacrit | epoetin zeta | Hospira | Authorised | Dez 07 |
| | Silapo | epoetin zeta | Stada | Authorised | Dez 07 |
| 3 | Benepali | etanercept | Samsung | Authorised | Jan 16 |
| | Erelzi | etanercept | Sandoz | Authorized | Jun 17 |
| 4 | Accofil | filgrastim | Accord | Authorised | Sep 14 |
| | Biograstim | filgrastim | AbZ-Pharma | ~~Withdrawn~~ | Sep 08 |
| | Filgrastim Hexal | filgrastim | Hexal AG | Authorised | Feb 09 |
| | Filgrastim ratiopharm | filgrastim | Ratiopharm | ~~Withdrawn~~ | Sep 08 |
| | Grastofil | filgrastim | Apotex | Authorised | Okt 13 |
| | Nivestim | filgrastim | Hospira | Authorised | Jun 10 |
| | Ratiograstim | filgrastim | Ratiopharm | Authorised | Sep 08 |
| | Tevagrastim | filgrastim | Teva | Authorised | Sep 08 |
| | Zarzio | filgrastim | Sandoz | Authorised | Feb 09 |
| 5 | Bemfola | follitropin alfa | Gedeon Richter | Authorised | Mrz 14 |
| | Ovaleap | follitropin alfa | Teva | Authorised | Sep 13 |
| 6 | Flixabi | infliximab | Samsung | Authorised | Mai 16 |
| | Inflectra | infliximab | Hospira | Authorised | Sep 13 |
| | Remsima | infliximab | Celltrion | Authorised | Sep 13 |
| 7 | Abasaglar | insulin glargine | Eli Lilly | Authorised | Sep 14 |
| | Lusduna | insulin glargine | MSD | Authorised | Jan 17 |
| | Solumarv | insulin human | Marvel Lifescience | ~~Refused~~ | - |
| | Alpheon | interferon alfa | BioPartners | ~~Refused~~ | - |
| 8 | Truxima | rituximab | Celltrion | Authorized | Feb 17 |
| | Blitzima | rituximab | Celltrion | authorized | Jul 17 |
| | Rixathon | rituximab | Sandoz | authorized | Jun 17 |
| | Riximyo | rituximab | Sandoz | authorized | Jun 17 |
| | Ritemvia | rituximab | Celltrion | authorized | Jul 17 |
| | Rituzena | rituximab | Celltrion | authorized | Jul 17 |
| 9 | Omnitrope | somatropin | Sandoz | Authorised | Apr 06 |
| | Valtropin | somatropin | BioPartners | ~~Withdrawn~~ | Apr 06 |
| 10 | Movymia | teriparatide | STADA | Authorised | Jan 17 |
| | Terrosa | teriparatide | Gedeon Richter | Authorised | Jan 17 |
| 11 | Amgevita | adalimumab | Amgen Europe B.V. | Authorised | Mar 17 |
| | Solymbic | adalimumab | Amgen Europe B.V. | Authorised | Mar 17 |
| | Imraldi | adalimumab | Samsung | Authorised | Aug-17 |

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# Changes in the manufacturing process of biologicals occur frequently

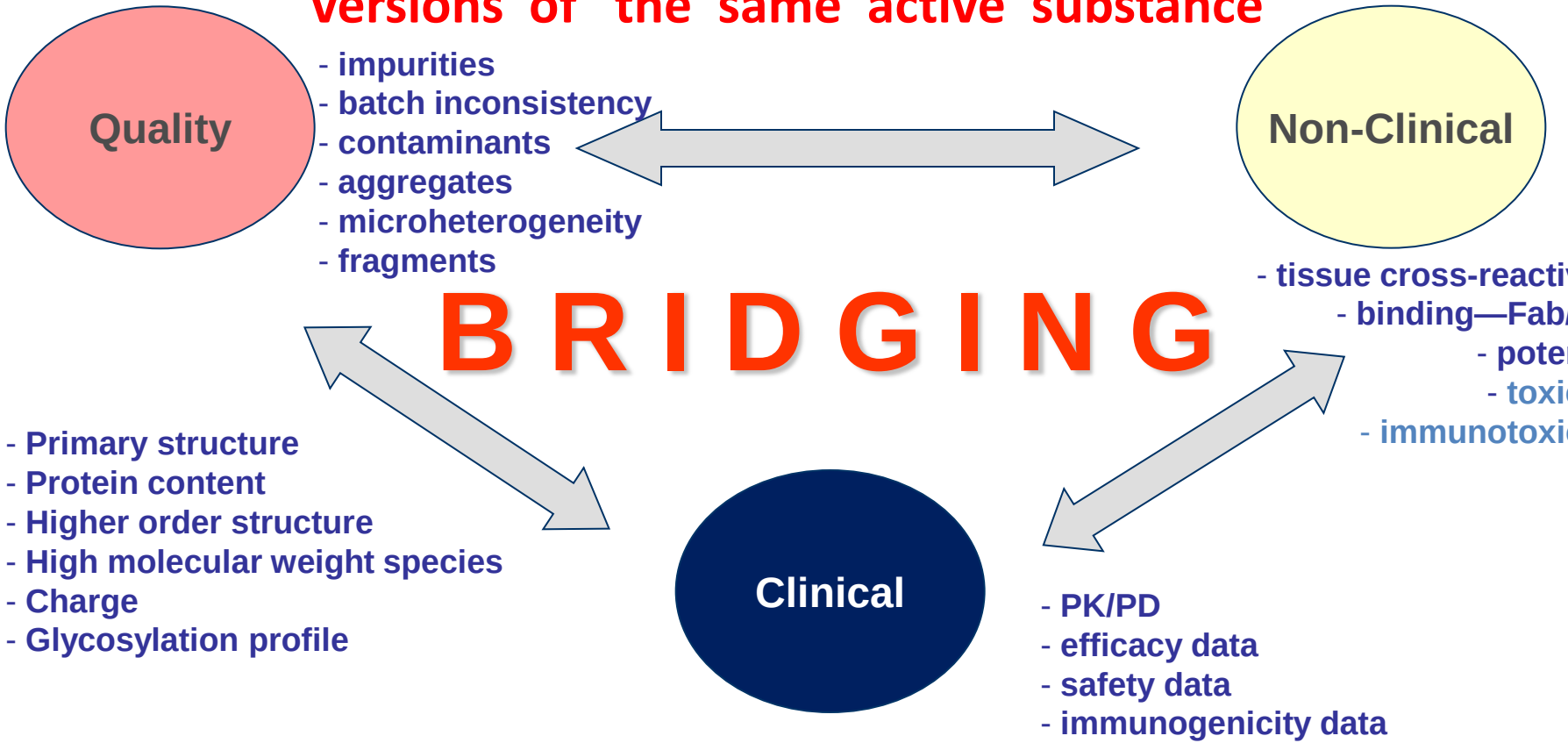
## → Concept  is not new!

- **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



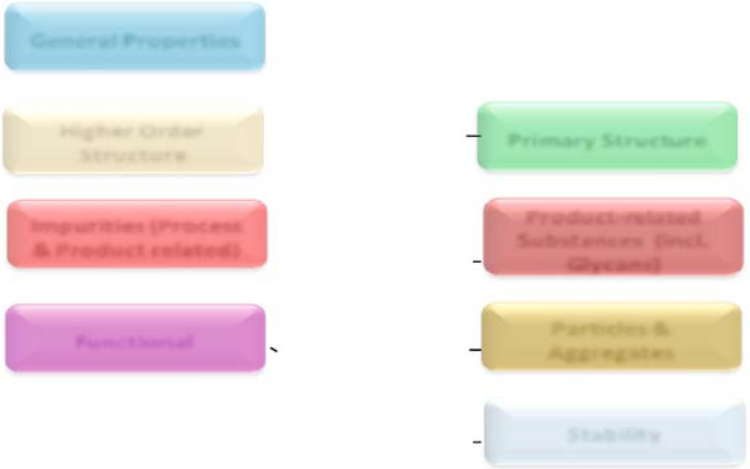
# Manufacturing changes authorized by EMA

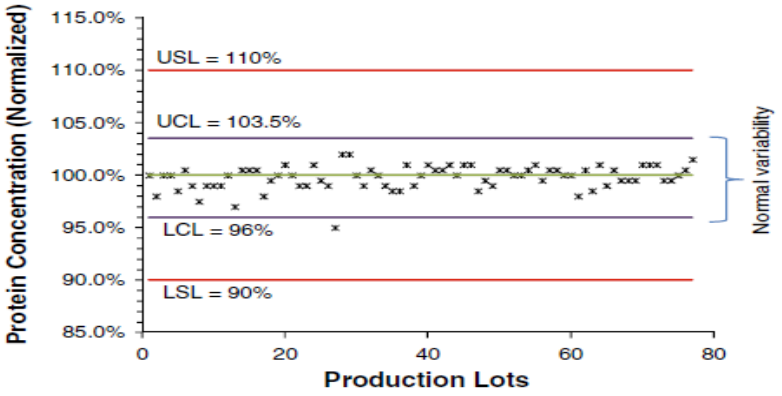
(EPARs of 29 Mabs: Total manufacturing changes = 404)

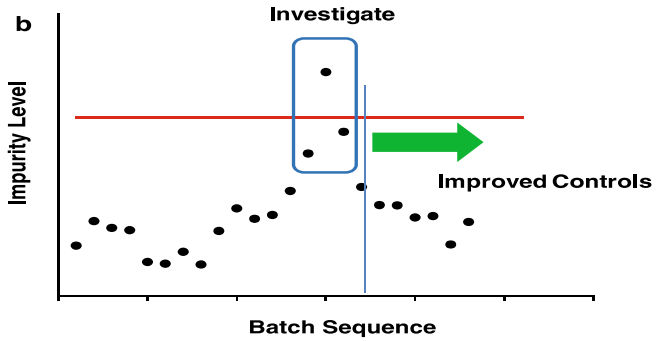

- New manufacturer of active substance (AS)
- Change of in process tests with widening of limits
- Change purification process of active substance (AS)
- Manufacturing change known to impact mechanism of action

*Vezér B, Buzás Zs, Sebeszta M, Zrubka Z.: Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents. Curr Med Res Opin. 2016 May;32(5):829-34*

# Manufacturing of biologics has inherent variability




en deviation (shift). **b** Drift in host cell impurity due to an interaction between raw materials and process parameters

## Need to

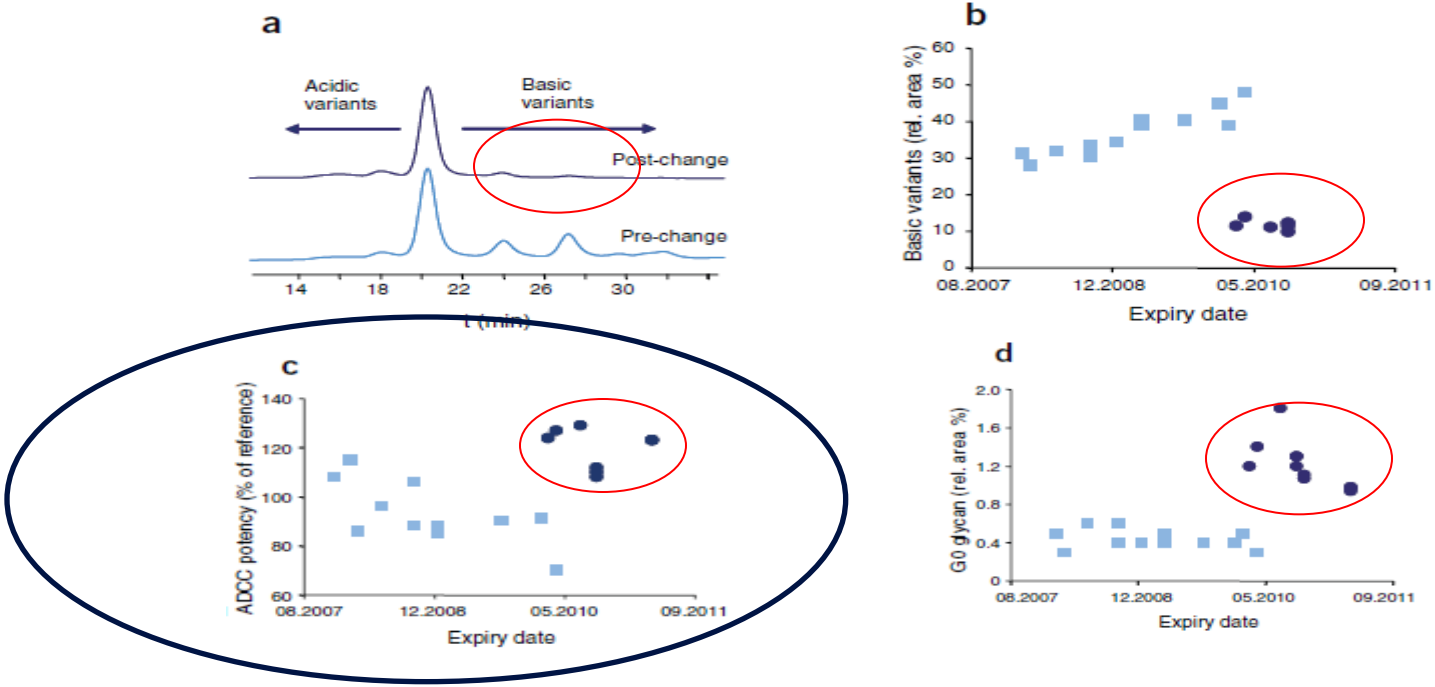
- define measurable product quality attributes
- Set specifications
- define proven acceptable ranges



Drift, Evolution, and Divergence in Biologics and Biosimilars Manufacturing Ramana, S.; Grampp, G. BioDrugs (2014) 28:363–372

# 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)



Schiestl, Nature Biotechnology Vol. 29 ; 4 , 2011

# Manufacturing changes authorized by EMA

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

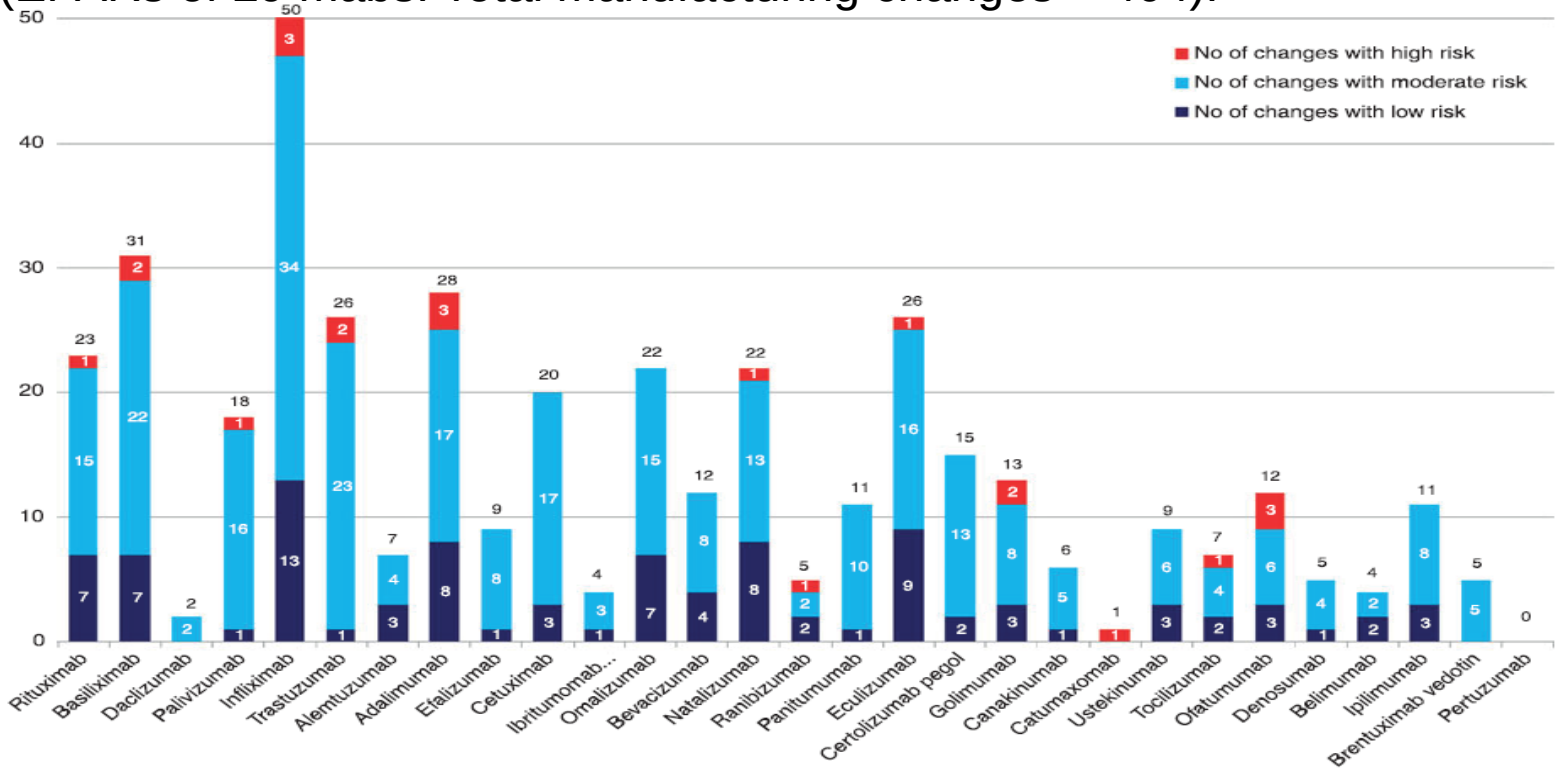



**Figure 2.** Number of manufacturing changes for monoclonal antibodies in their European Public Assessment Reports according to risk category (during the search period all non-proprietary names relate only to the trade named medicines listed in Table 1).

*Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents.*
*Vezér B, Buzás Zs, Sebeszta M, Zrubka Z.: Curr Med Res Opin. 2016 May;32(5):829-34*

# 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.

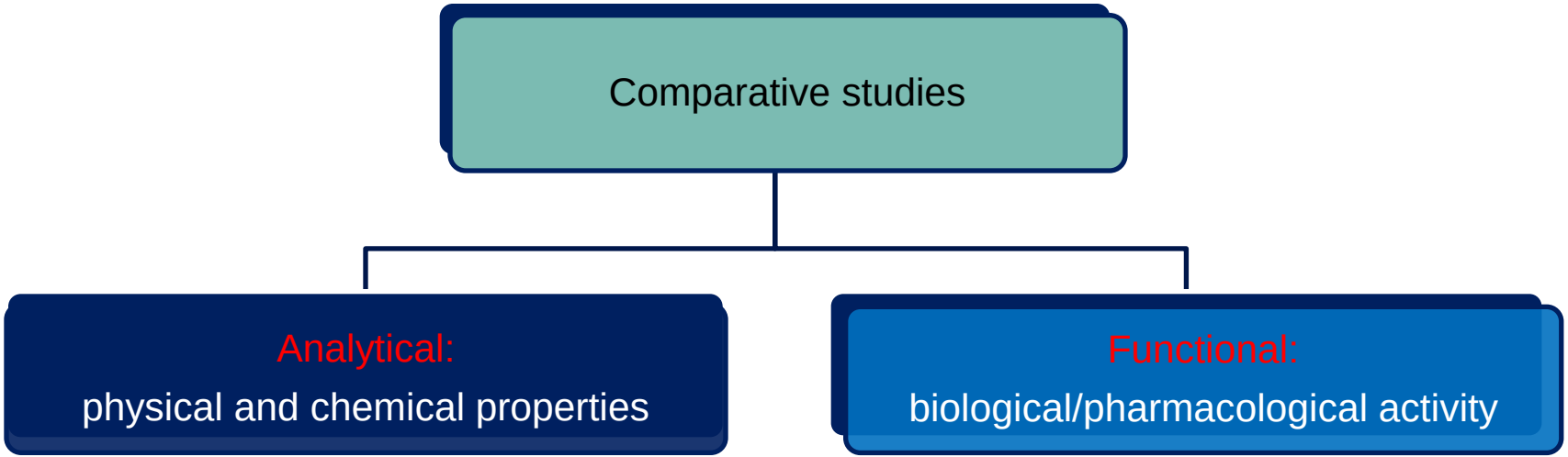
# Summary: Changes in the manufacturing process of biologicals occur frequently

## → 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.**"

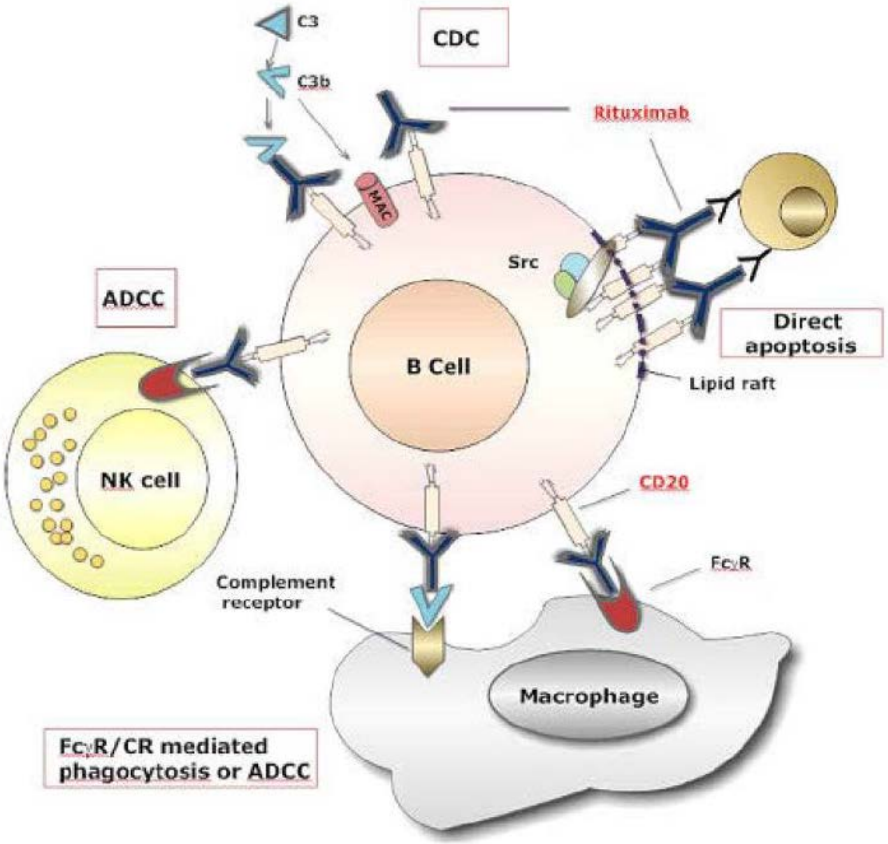
# Example: Establishing Biosimilarity with Comparability studies  Truxima versus MabThera –



# Comparability studies Truxima versus MabThera – Overview of comparative quality studies

| Molecular parameter | Methods for control and characterisation | Key findings |
|---|---|---|
| Primary structure | Amino acid analysis<br>Molar absorptivity<br>N-terminal sequencing<br>C-terminal sequencing<br>Peptide mapping by HPLC<br>Determination of intact mass | Identical primary structure<br>Intact mass comparable |
| Secondary and higher order structure | Fourier Transform Infra-Red spectroscopy<br>Circular Dichroism<br>Differential Scanning Calorimetry | Highly similar secondary and higher order structure.<br>• Similar post-translational modifications included deamidation, oxidation and C-terminal lysine variants,<br>• Highly similar number and distribution of charged variants<br>• highly similar glycosylation profiles,<br>• highly similar monosaccharide (Fucose, N-acetyglucosamine, Galactose and Mannose) sugar contents<br>• Highly similar sialic acid (N-acetylneuraminic acid (NANA) contents<br>• 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

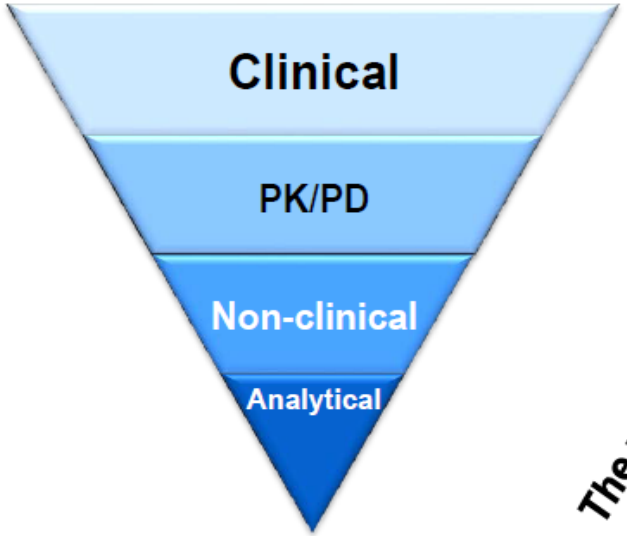
CD20 levels on the B cell surface, and B cell count differ largely between NHL and Rheumatoid Arthritis (RA) patients due to the range of tumour burden among patients.

# Comparability studies Truxima versus MabThera – Overview of comparative preclinical studies

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

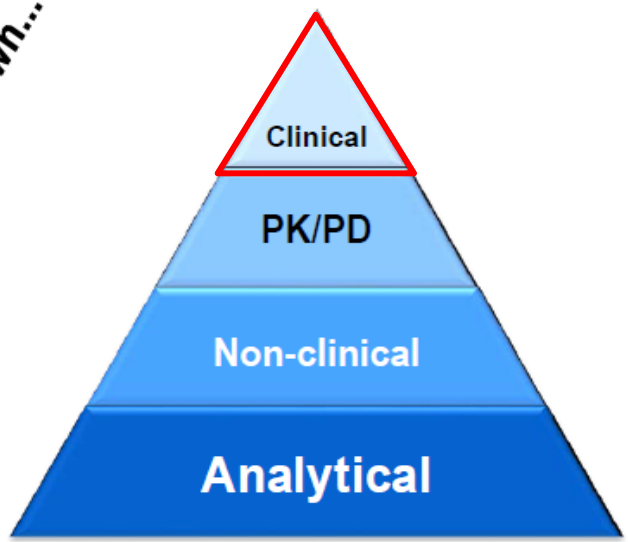
# Implication 1: Paradigm Shift

Originals, Biobetters




The world turned upside down…

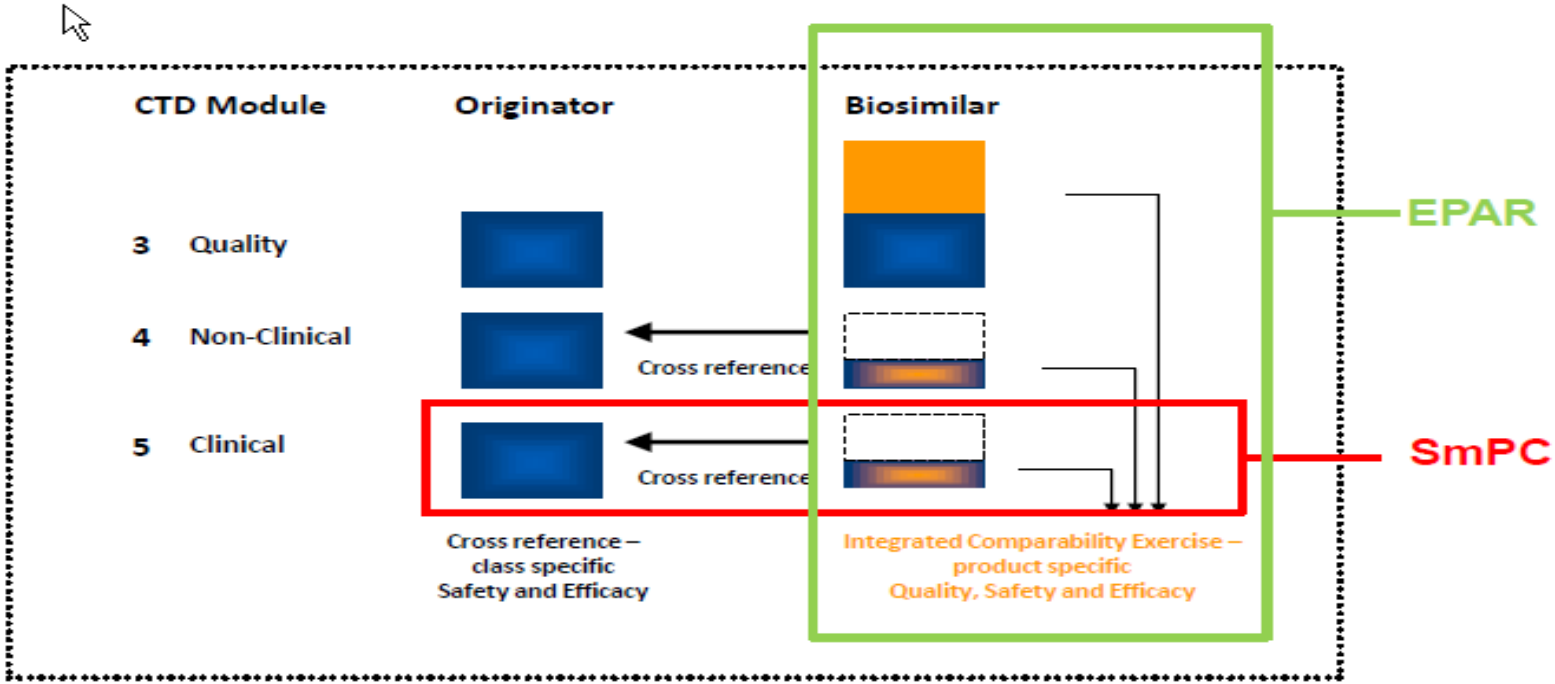
Biosimilars




## „Totality of evidence“

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

# Implication 2: Source of Information for Biosimilars is European Public Assessment Report (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

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- Different safety profile in different therapeutic indications

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

# Considerations for extrapolation

## MYL-1401O, a proposed biosimilar to US-Herceptin

## www.fda.gov published July 13, 2017

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, ABP 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

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

## 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.**



→ Different EU and US nomenclature hampers debate

# Interchangeability: Theoretical considerations

## Changes in the manufacturing process of biologicals are ongoing

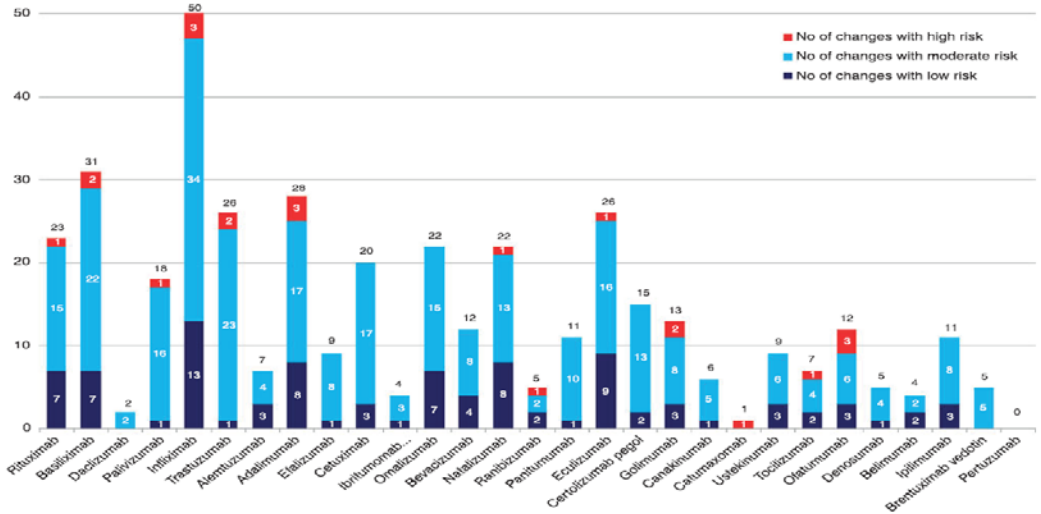


**Figure 2.** Number of manufacturing changes for monoclonal antibodies in their European Public Assessment Reports according to risk category (during the search period all non-proprietary names relate only to the trade named medicines listed in Table 1).

## … in real life:

Different versions of same active substance

are de facto already being used <u>interchangeably</u>

without necessity for clinical studies

BioDrugs
DOI 10.1007/s40259-017-0227-4

CURRENT OPINION

# A 'Global Reference' Comparator for Biosimilar Develop

Christopher J. Webster[1] · Gillian R. Woollett[2]



**Abstract** Major drug regulators have indicated in guidance their flexibility to accept some development data for biosimilars generated with reference product versions licensed outside their own jurisdictions, but most authorities require new bridging studies between these versions and the versions of them licensed locally. The costs of these studies are not trivial in absolute terms and, due to the multiplier effect of required repetition by each biosimilar sponsor, their collective costs are substantial. Yet versions of biologics licensed in different jurisdictions usually share the same development data, and any manufacturing changes between versions have been justified by a rigorous comparability process. The fact that a biosimilar is usually expected to be licensed in multiple jurisdictions, in each case as similar to the local reference product, confirms that minor analytical differences between versions of reference biologics are typically inconsequential for clinical outcomes and licensing. A greatly simplified basis for selecting a reference comparator, that does not require conducting new bridging studies, is proposed and justified based on the shared data of the reference product versions as well as the proof offered where biosimilars have already been approved. The relevance of this proposal to the interchangeability designation available in the US is discussed.

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[2] FDA Regulatory Strategy and Policy, Avalere Inc, 1350 Connecticut Avenue, NW, Suite 900, Washington, DC 20036, USA

Published online: 19 May 2017

**Key Points**

Bridging studies betwee
of an originator biologic
biosimilar development
benefit or scientific rig
biosimilar. Moreover,
discretion of local reg

The authors propose
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## 1 Introd

The effic
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# Toward Interchangeable Biologics

McCamish[1], J Pakulski[2], C Sattler[3] and G Woollett[4]

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edicines Agency is

comfortable calling both approaches comparability, whereas the FDA distinguishes the two. Nonetheless, both settings invoke the "highly similar" analytical standard for the two products that are being compared (biosimilar to reference vs. pre to post-manufacturing change products), and both require an increasingly comprehensive understanding of structure-function relationships in order for the determination of "no clinically meaningful differences" to be accepted absent complete clinical studies in every indication. Immunogenicity studies are an additional consideration for biosimilars and particularly "interchangeable" biologics although generally not required before a manufacturing change.

Enoxaparin is used in critical care indications with lethal consequence if the product does not work. In approving enoxaparin as a fully substitutable complex generic drug of biologic origin in 2010, the FDA identified five criteria for addressing "sameness" in lieu of comparative clinical trials (including physicochemical attributes and fragmentation methods; sourcing; nature and arrangement of components; anticoagulant assays, and human responses).[3] Biosimilars utilize a different regulatory pathway (351(k)), but ultimately approval and interchangeability requires the same confidence that the biosimilar has the "same" active pharmaceutical ingredient as the reference product, and can be switched without impact on the patient. FDA guidance on interchangeability is not yet available. Data expected will likely include "switching studies" in patients, while monitoring immunogenicity, demonstrating no difference compared to no switching.

## DEVELOPMENT OF A BIOSIMILAR/INTERCHANGEABLE BIOLOGIC

### Analytical studies provide the basis for a determination of biosimilarity

The "design space" for a biosimilar is created by the biosimilar sponsor's in-depth analysis of multiple lots of their chosen reference product. This provides the specifications for the biosimilar and the justification for clinical acceptability when the biosimilar product attributes fall within the ranges of each analytical attribute of the reference product.

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4; advance online publication 00 Month 2014. doi:10.1002/cpt.39

# 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

| *Product* | Total , n | Identifiable product , n (%) | |
|---|---|---|---|
| etanercept | *19,716* | 19,012 | 96.4% |
| infliximab | *12,045* | 11,342 | 94.2% |
| insulin glargine | *2,446* | 2,364 | 96.6% |
| filgrastim | *1,043* | 934 | 89.5% |
| epoetin alfa | *1,084* | 1,045 | 96.4% |
| somatropin | *1,047* | 1,006 | 96.1% |
| follitropin alfa | *448* | 442 | 98.7% |

95.5% overall

# EMA Pharmacovigilance Project 2017: ongoing
## Biological product identifiability in EudraVigilance (EV)

- 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
  - ✓ Vermeer NS et al (2013) Traceability of biopharmaceuticals in spontaneous reporting systems: a cross sectional study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance databases. Drug Safety 2013; 36:617–625

**We can be confident in our Pharmacovigilance system !**

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# Thanks for your attention !