European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

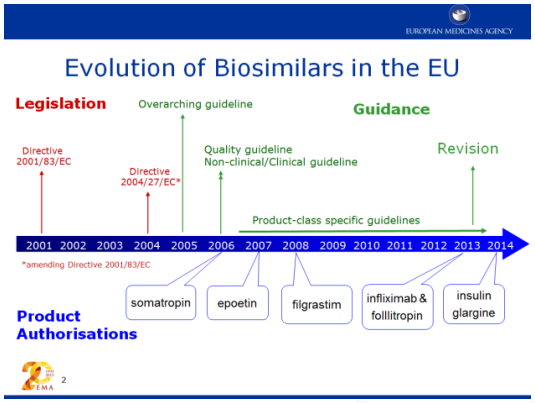
BIOSIMILARS: SATELLITE SESSION

Biosimilars – the regulatory framework

Background and interface of quality assessment with quality standards

Presented by: Peter Richardson, 08 February 2017
Head of Quality Office
Human Medicines R&D Support Division.

Biosimilars: A brief history



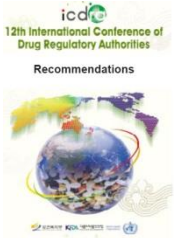
80's : rDNA insulin

90's : Comparability guidelines

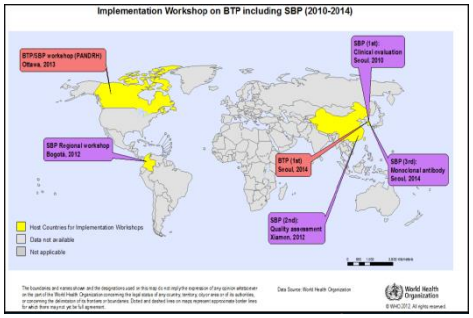
00's : EU + WHO Biosimilar guidelines

2016 : Strong global interest in biosimilars

WHO – Similar Biotherapeutic Products (SBP)



- ICDRA 2006
- Implementation meetings
- SBP Guideline: TRS 977, 2009
- SBP mAb Guideline: ECBS 2016



WHO guideline: very important tool to assist global convergence

World Health Organization

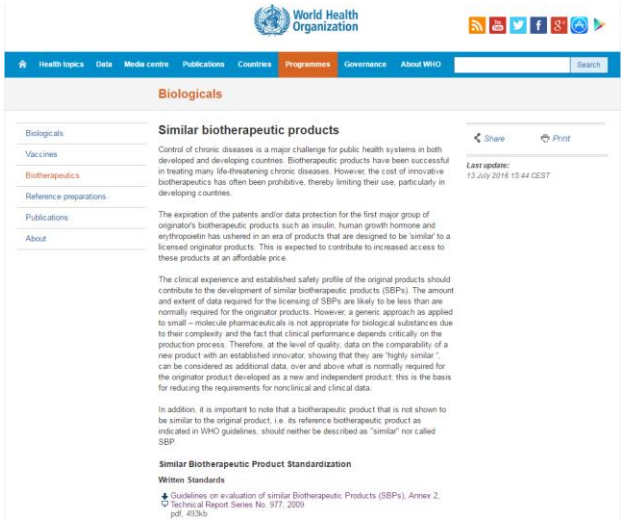
WHO/BS/2016.2290
ENGLISH ONLY

Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs)

NOTE:
This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the proposed Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs) to a broad audience and to improve transparency of the consultation process.

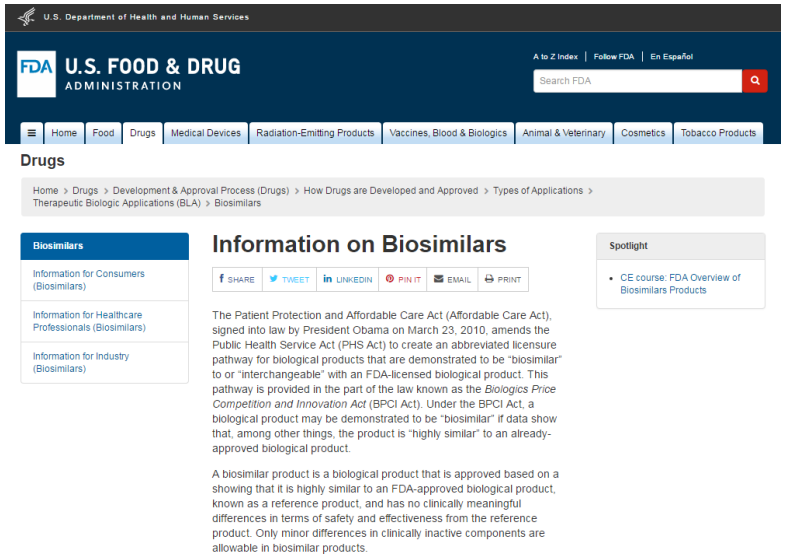
The text in its present form does not necessarily represent an agreed formulation of the Expert Committee. Written comments proposing modifications to this text MUST be received by 16 September 2016 in the Comment Form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Essential Medicines and Health Products (EMP). Comments may also be submitted electronically to the Responsible Officer: Dr Kai Gao at email: gaok@who.int.

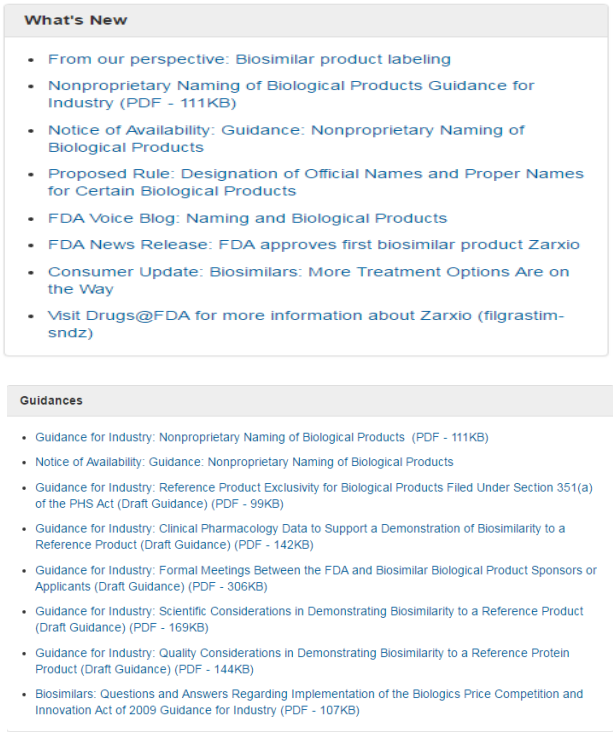
The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide" (WHO/IMD/PUB/04.1).



US FDA – Biosimilars, 2016

Guidelines adopted; 2015 1st biosimilar: Zarxio approved.





Advisory Commitees: Briefing Documents, e.g. filigrastim, etanercept

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM428780.pdf

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM510493.pdf

Regulatory Convergence –

Biologicals / Biosimilars

- EU guidelines and experience continue to be important reference for other Competent Authorities
- EU supports further development / implementation of WHO SBP guidelines
- Liaison with international partners (e.g. via International Pharmaceutical Regulators Forum – IPRF BWG, also Biosimilar Cluster EMA/FDA/HC/PMDA)
- Parallel scientific advice / ad hoc discussions
- Quality standards (e.g. monograph requirements):

  increase transparency

Biosimilar Product Review (Jan 2017) *

57 MAAs submitted

40 MAAs post-review

17 MAAs under review

2 Negative

Interferon alfa
Insulin

28 Positive

26 Valid MAs

Somatropin (1)
Epoetin (5)
Filgrastim (8)
Infliximab (3)
Follitropin alfa (2)
Etanercept (1)
Insulin glargine (2)
Enoxaparin (2)
Teriparatide (2)

10 Withdrawn

Insulin (6)
Epoetin (1)
Pegfilgrastim (3)

2 Withdrawn

Filgrastim (1)
Somatropin (1)

Adalimumab (2)
Bevacizumab (2)
Etanercept (1)
Insulin glargine (1)
Insulin lispro (1)
Pegfilgrastim (2)
Rituximab (2)
Trastuzumab (3)

Awaiting EC decision

Adaliumumab (2)
Rituximab (1)

* Information on EMA website

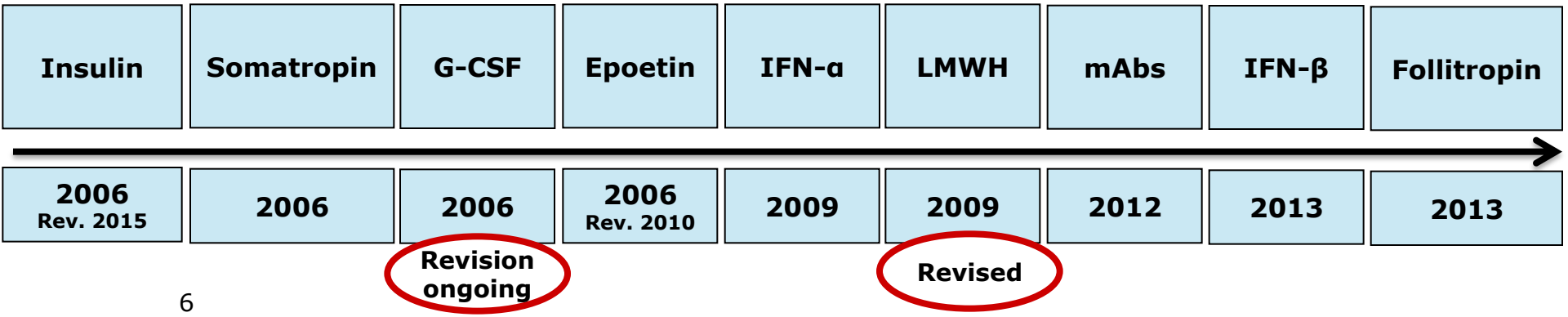
EU Guidelines for biosimilars

General Guidelines:

Overarching Guideline (CHMP/437/04 Rev. 1)
"Guideline on Similar Biological Medicinal Products"

Non-clinical/clinical Guideline	Quality Guideline

Class-specific Guidelines: non-clinical/clinical aspects:

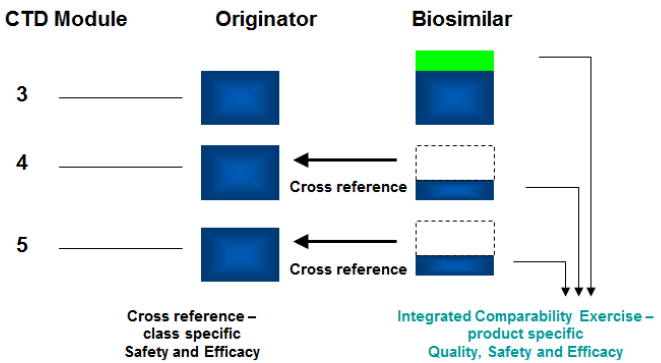


Biosimilar guidelines: evolution in EU

- Initally: conservative on clinical

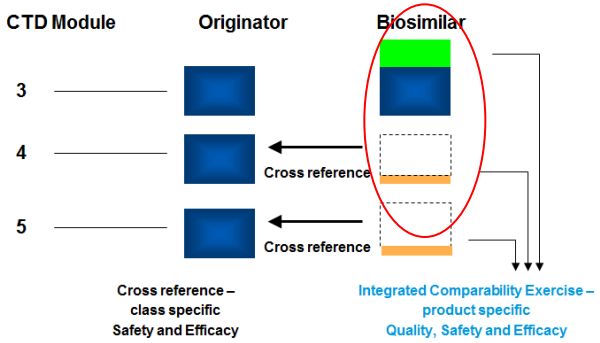
(e.g. epoetin: 2 studies required in titration and maintenance)

+ emphasis on animal studies.



- Now: use of PD markers for clinical, relevant non-clinical in-vivo study

+ increased value from detailed quality (characterisation).



Biosimilars – general principles

(see guideline for complete information)

General definition

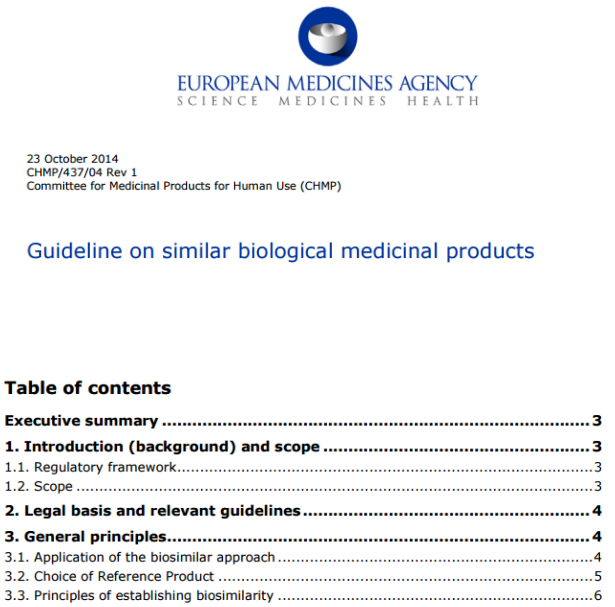
A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established.

Biosimilars are not generics

- The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) which is applicable to most chemically-derived medicinal products is in principle not sufficient to demonstrate similarity of biological/biotechnology-derived products due to their complexity. The biosimilar approach, based on a comprehensive comparability exercise, will then have to be followed.

Authorised biosimilar is an independent product

- There is no regulatory requirement to repeat the demonstration of biosimilarity against the reference product, e.g. in the context of a change in the manufacturing process, once the Marketing Authorisation has been granted.



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23 October 2014
CHMP/437/04 Rev 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products

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EMA Biosimilars: quality guideline

(revised in 2013)

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SCIENCE MEDICINES HEALTH

22 May 2014
EMA/CHMP/BWP/247713/2012
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)

State-of-art analytical characterisation

Guideline ≠ Checklist or "recipe"

Manufacturing process - well developed

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Quality guideline

- Facilitate a global development approach
- Quality target product profile (QTPP) should be established early in development
- Acknowledge that the quality of both biosimilar and reference product may evolve through their life-cycle
- Focus on comparability at the level of product
- Amino acid sequence same as reference product
- Section on immunochemical properties introduced to cover additional testing expected for mAbs
- Possibility for different expression system, however caution raised if there are differences in quality profile

EMA Biosimilars: quality guideline

(EMA/CHMP/BWP/247713/2012)

Biosimilar = Comparability Exercise with Reference Product

Comparability Exercise = comparative characterisation

EU guideline: Characterisation data ≠ Monograph

A comparison of the biosimilar to a publicly available standard, e.g. a pharmacopoeial monograph, is not sufficient for the purpose of comparability. The biosimilar should be demonstrated to be similar to a reference medicinal product approved in the Community, which is selected by the company developing the biosimilar. Consequently, an extensive comparability exercise with the chosen reference medicinal product will be required to demonstrate that the biosimilar product has a similar profile in terms of quality, safety and efficacy to the reference medicinal product.

EU guideline: Ref. Std. ≠ Reference Product

Publicly available reference standards (e.g. Ph. Eur.) cannot be used as the reference medicinal product for demonstration of biosimilarity. However, as discussed in section 5.3 below, the use of these standards plays an important role in method qualification and standardisation.

Biosimilar = biological medicinal product;

Relevant guidelines apply, e.g. ICH Q6B

Specifications

Specifications are one part of a total control strategy designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterisation during development, upon which many of the specifications are based, adherence to Good Manufacturing Practices, a validated manufacturing process, raw materials testing, in-process testing, stability testing, etc.

2.4 Pharmacopoeial Specifications

Pharmacopoeias contain important requirements pertaining to certain analytical procedures and acceptance criteria, which, where relevant, are part of the evaluation of either the drug substance or drug product. Such monographs, applicable to biotechnological and biological products, generally include, but are not limited to tests for sterility, endotoxins, microbial limits, volume in container, uniformity of dosage units and particulate matter. With respect to the use of pharmacopoeial methods and acceptance criteria, the value of this guidance is linked to the extent of harmonisation of the analytical procedures of the pharmacopoeias. The pharmacopoeias are committed to developing identical or methodologically equivalent test procedures and acceptance criteria.

European Medicines Agency

September 1999
CPMP/ICH/365/96

ICH Topic Q 6 B
Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

Step 5

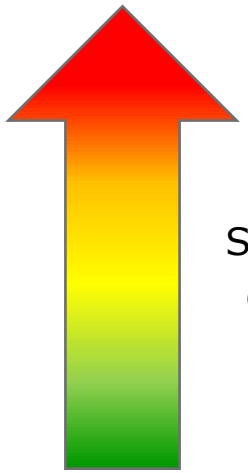
NOTE FOR GUIDANCE ON
SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS
(CPMP/ICH/365/96)

TRANSMISSION TO CPMP	February 1998
RELEASE FOR CONSULTATION	February 1998
DEADLINE FOR COMMENTS	July 1998
FINAL APPROVAL BY CPMP	March 1999
DATE FOR COMING INTO OPERATION	September 1999

Quality – the foundation of biosimilars:

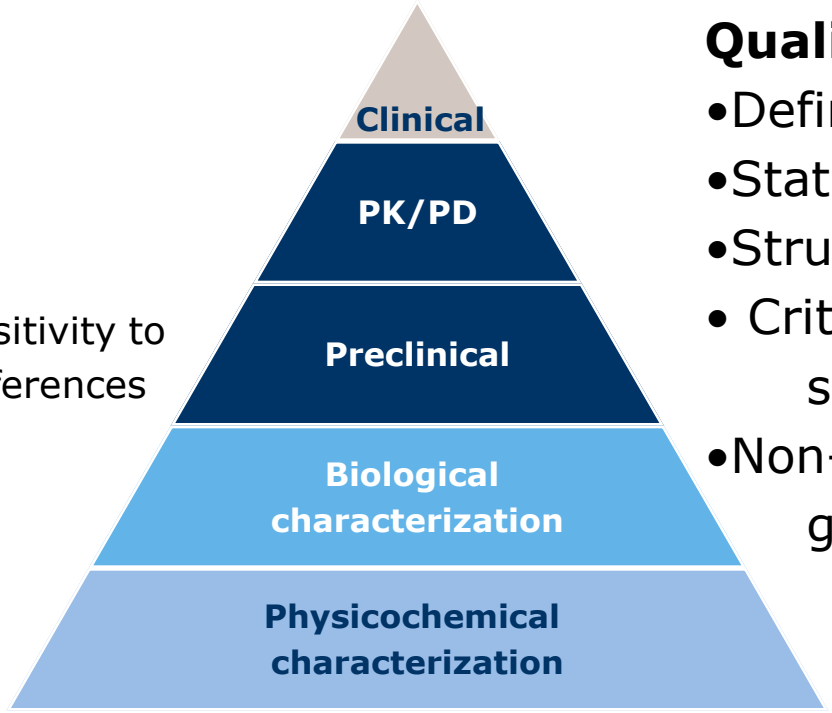
highly structured development

Lower



Higher

Sensitivity to differences



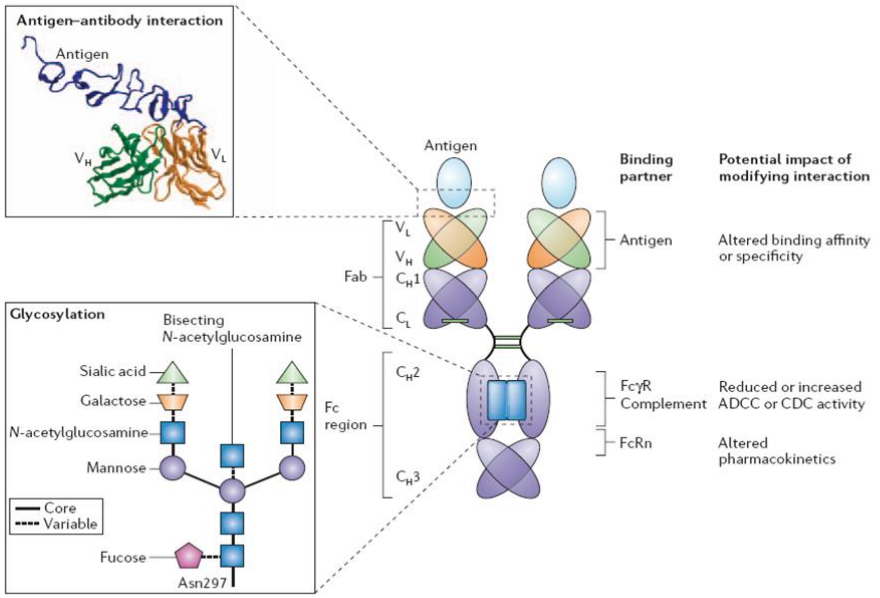
Quality

- Define Target Profile
- State of art analytical tools
- Structured development: QbD
- Critical Quality Attributes – systematically Controlled
- Non-critical attributes – greater tolerance

Complex Substances: biosimilar assessment v quality standard

Molecules of increased complexity – require increased analytical characterisation. This puts strain on content of a monograph (e.g. too much information).

Complexity of monoclonal antibodies



Carter PJ: Potent antibody therapeutics by design, Nature Rev Immunol 6, 343 (2006)

Christian K Schneider

ICH Q6B: Further definitions

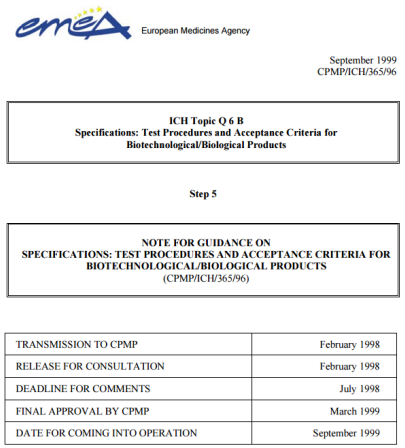
Heterogeneity

An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic processes used by living organisms to produce them; therefore, the desired product can be a mixture of anticipated post-translationally modified forms (e.g., glycoforms).

Heterogeneity can also be produced during manufacture and/or storage of the drug substance or drug product. Since the heterogeneity of these products defines their quality, the degree and profile of this heterogeneity should be characterised, to assure lot-to-lot consistency. When these variants of the desired product have properties comparable to those of the desired product with respect to activity, efficacy and safety, they are considered product-related substances. When process changes and degradation products result in heterogeneity patterns which differ from those observed in the material used during preclinical and clinical development, the significance of these alterations should be evaluated.

Analytical methods to elucidate physicochemical properties are listed in Appendix 6.1. New analytical technology and modifications to existing technology are continually being developed and should be utilised when appropriate.

For the purpose of lot release (section 4), an appropriate subset of these methods should be selected and justified.



European Medicines Agency

September 1999
CPMP/ICH/365/96

ICH Topic Q 6 B
Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

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mAb case study – Quality Profile

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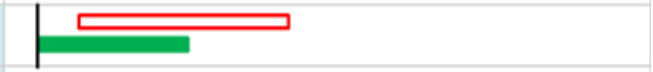
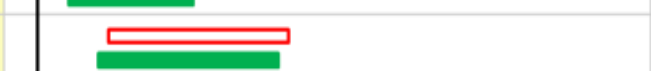
Quality attribute	Product	Min/max ranges	Bar diagram
G0F-GlcNac	Reference Biosim candidate	0.05 – 0.3 % 0.00 – 0.2 %	
G0	Reference Biosim candidate	1.2 – 2.1 % 1.5 – 2.0 %	
G0F	Reference Biosim candidate	20.3 – 32.1 % 25.3 – 33.0 %	
Man5	Reference Biosim candidate	0.0 – 0.9 % 0.2 – 0.5 %	
(1,6)G1F	Reference Biosim candidate	2.5 – 4.1 % 3.0 – 3.9 %	
(1,3)G1F	Reference Biosim candidate	1.6 – 2.3 % 1.7 – 2.2 %	
G2F	Reference Biosim candidate	10.5 – 25.7 % 11.0 – 24.4 %	
G2FS1	Reference Biosim candidate	35.3 – 39.1 % 36.2 – 38.5 %	
G2FS2	Reference Biosim candidate	11.4 – 13.2 % 11.4 – 13.0 %	
NGNA	Reference Biosim candidate	3.3 – 5.5 % 1.1 – 2.0 %	
Deamidation	Reference Biosim candidate	0.9 – 2.4 % 0.3 – 1.5 %	
Oxidation	Reference Biosim candidate	1.2 – 4.3 % 1.0 – 4.1 %	
Dimer	Reference Biosim candidate	0.0 – 2.1 % 0.0 – 0.8 %	
Higher aggregates	Reference Biosim candidate	0.0 – 0.8 % 0.0 – 0.2%	
Binding assay	Reference Biosim candidate	91 – 108 % 93 – 105 %	
CDA activity	Reference Biosim candidate	84 – 110 % 90 – 111 %	
ADCC activity	Reference Biosim candidate	75 – 132 % 82 – 115 %	

Quality

- QbD – Risk Analysis
- Determine CQAs
- Control Operating Ranges for CQAs
- Non-Critical attributes – less stringent control

Outcome

- Biosimilar: high level of control and similarity to originator product

Ref: Schiestl, et al., Biologicals 42 (2014) 128-132

Monoclonal Antibody variants : QTTP & Lifecycle

Manufacturing Process can affect quality profile

Regulatory Assessment: review comparability – meaningful differences ?

For a monograph – very wide limits may be required (or none)

New approaches applied in recent Monographs

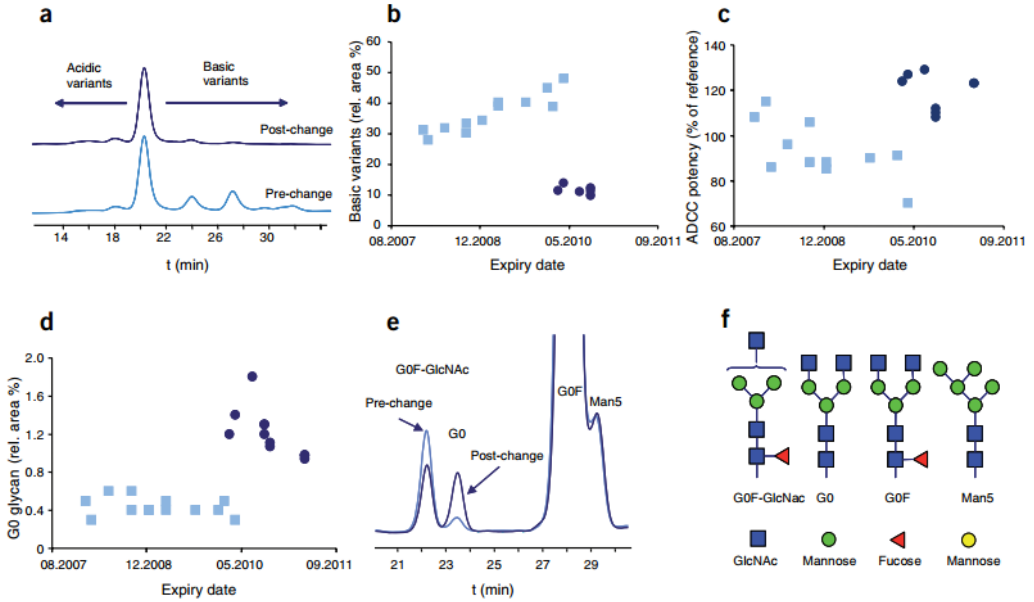


Figure 2 Comparison of the different pre- and post-change batches of Rituxan/Mabthera. **(a)** Exemplary CEX chromatograms. **(b)** Amount of basic variants of the pre-change ($n = 12$) and post-change ($n = 6$) batches as measured by CEX. **(c)** ADCC potency of the pre-change ($n = 11$) and post-change ($n = 8$) batches. **(d)** Relative amount of the G0 glycan of the pre-change ($n = 13$) and post-change ($n = 11$) batches. **(e)** Exemplary glycan mapping chromatograms. **(f)** Glycan legend.

Schiestl M et. al, : Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceuticals, Nature Biotechnology 29, 310-312 (2011)

Trends from scientific advice procedures

- ✓ Focus on efficient / robust data sets : quality basis with informative nonclinical / clinical studies
- ✓ Global development : use of non-EU comparator
- ✓ Explore use of statistical methodology for comparative assessment of quality attributes
- ✓ Greater integration of quality data:

  Impact on S/E data requirements.

  (EMA pilot starting Feb 2017)

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/12/WC500218206.pdf

Statistical methodology for quality comparability

- Triggered by increasing number of scientific advice requests
- Increasingly, biosimilar SA requests include discussion on statistical methodology for quality aspects
- Reflection paper may cover biosimilar development and comparability evaluation (ICH Q5E) and discuss methodologies
- Challenges: Limited number of batches + diversity of critical quality attributes

30 May 2013
EMA/CHMP/297149/2013 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for a reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

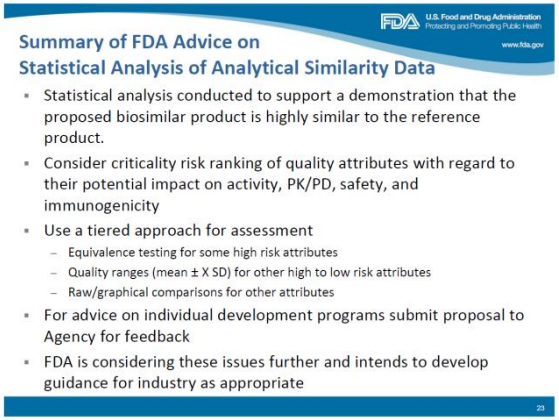
Agreed by Biostatistics Working Party	March 2013
Adoption by CHMP for release for consultation	30 May 2013
Start of public consultation	28 June 2013
End of consultation (deadline for comments)	30 September 2013

Comments should be provided using this template. The completed comments form should be sent to Biostatistics@ema.europa.eu.

Keywords	*statistical methodology, quality attributes, equivalence testing, biosimilar, biological product*

Summary of FDA Advice on Statistics for Analytical Similarity Assessment for a Proposed Biosimilar

- Evaluate quality attributes consistent with risk assessment principles in ICH Quality Guidelines Q8, Q9, Q10, and Q11.
- Consider risk ranking of CQAs with regard to their potential impact on activity, PK/PD, safety, and immunogenicity
- Use a tiered approach for assessment
  - Equivalence testing for some high risk attributes
  - Quality ranges (mean ± X SD) for other high to low risk attributes
  - Raw/graphical comparisons for other attributes
- Seek FDA advice on individual development programs
- FDA is considering these issues and intends to develop guidance as appropriate



From S. Kozlowski, DIA Meeting, Bethesda, Oct-15
L. Christl, ODAC, Jan-15

EU : current view on statistics for analytical similarity

The use of statistics for demonstrating analytical similarity

- Currently, the CHMP does not require nor recommend any specific statistical method for assessment of biosimilarity
  - EMA/CHMP/BWP/247713/201 "A descriptive statistical approach to establish ranges for quality attributes could be used"
- Proposals for statistical analysis are welcomed but should be justified in the dossier
  - QA criticality ranking (link to the overall statistical approach), assay considerations, level of the QA in the product etc.
  - Appropriateness and limitations of the statistical analysis
- Various factors can influence the outcome of statistical tests
  - Sample size (unit of observation), origin (sampling strategy, sources of variability) and distribution (normality)
  - Acceptance ranges and significance levels (uncertainty) chosen
  - Risk of false positive conclusion

DIA DEVELOP INNOVATE ADVANCE

The use of statistics for demonstrating analytical similarity

- Similarity ranges established based on tolerance intervals can lead to wide ranges with little (or no) clinical relevance
  - Depending on the chosen test (e.g. TI, PI, SD) and the data set available, the use of statistical intervals may result in an inability to detect relevant difference
- If inferential statistics is used, testing for equivalence is generally preferred
  - One-sided test could be acceptable for certain QAs (e.g. impurities)
- The final conclusion on analytical biosimilarity can not be drawn only based on statistical analyzes
  - Raw data should always be provided in a suitable format
  - A statistically insignificant difference could in principle be clinically significant -> a "tick box approach" is not possible

DIA DEVELOP INNOVATE ADVANCE

From N. Ekman, DIA Meeting, Bethesda, Oct-15

Overarching Guideline

"Global Development" option:

(i.e. Reference Product from non-EU area)

- Aim: Facilitate global development
- Reference product must be authorised in the EEA
- Comparability exercise: Non-EEA authorised comparator can be acceptable for certain clinical studies and *in-vivo* non-clinical studies, provided it is:
  - Authorised by regulatory authority with similar scientific/regulatory standards
  - Representative of the reference medicinal product (to be demonstrated by the applicant – bridging data required)

"For Demonstration of biosimilar comparability at the quality level, side-by-side analysis of the biosimilar product (from commercial scale and site) with EEA authorised reference product must be conducted. However, combined use of non-EEA authorised comparator and EEA authorised reference product is acceptable for the development of the Quality Target Product Profile of the biosimilar product."

Applicant to demonstrate that the comparator authorised outside the EEA is representative of the reference product authorised in the EEA.

Global development

Choice of reference product (RP):

- A non EEA-authorised version of the RP may be used for certain clinical and *in vivo* non-clinical studies if
  - Authorised based on similar scientific and regulatory standards as EMA
  - Representative of the RP in the EEA
- Bridging data

  must include
  - 3-way analytical comparison (structural and functional data)

  and *may* include
  - 3-way PK and/or PD comparison
- Comparable requirements in EU and US

Bridging study data: EP2006

Figure 3. Biological activity of EP2006, US-licensed Neupogen and EU-approved Neupogen

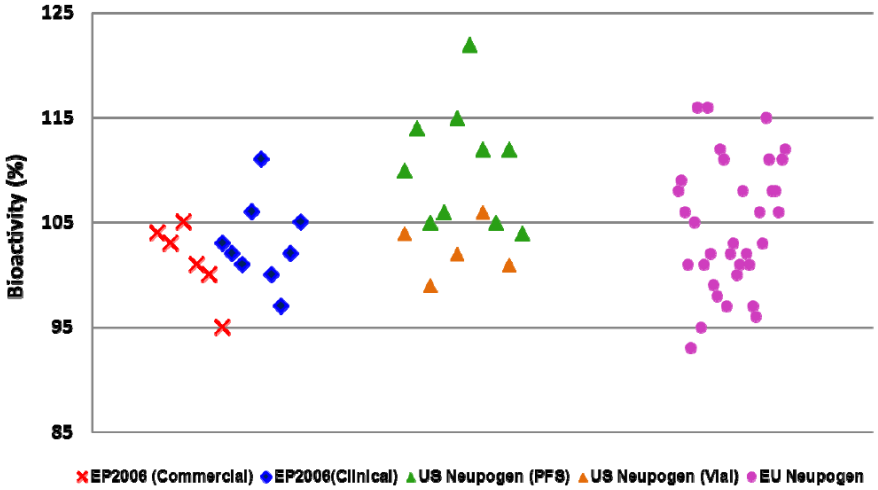


Table 2: Descriptive Statistics for Bioactivity (%)

Product	# batches	Min	Max	Mean	Standard Deviation	CV [a](%)
EP2006 (clinical and commercial, PFS)	15	95	111	102.3	3.81	3.72%
US-Neupogen (PFS and Vial)	15	99	122	107.8	6.21	5.76%
EU-Neupogen (PFS)	34	93	116	104.7	6.18	5.91%

[a] CV: coefficient of variability

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM428780.pdf
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM428781.pdf

Regulatory experiences on quality

- Biosimilars require state of the art characterisation.
- Quality is key – differences (at some level) always exist, i.e. heterogeneity expected / normal (may need justification).
- MAA assessment needs to be flexible and utilise a range of techniques to accommodate variability and determine that there are no relevant differences.
- Regulators ensure that a biosimilar is HIGHLY SIMILAR to the authorised originator (reference product).

Biological Medicinal Products

Quality : assured by a number of activities

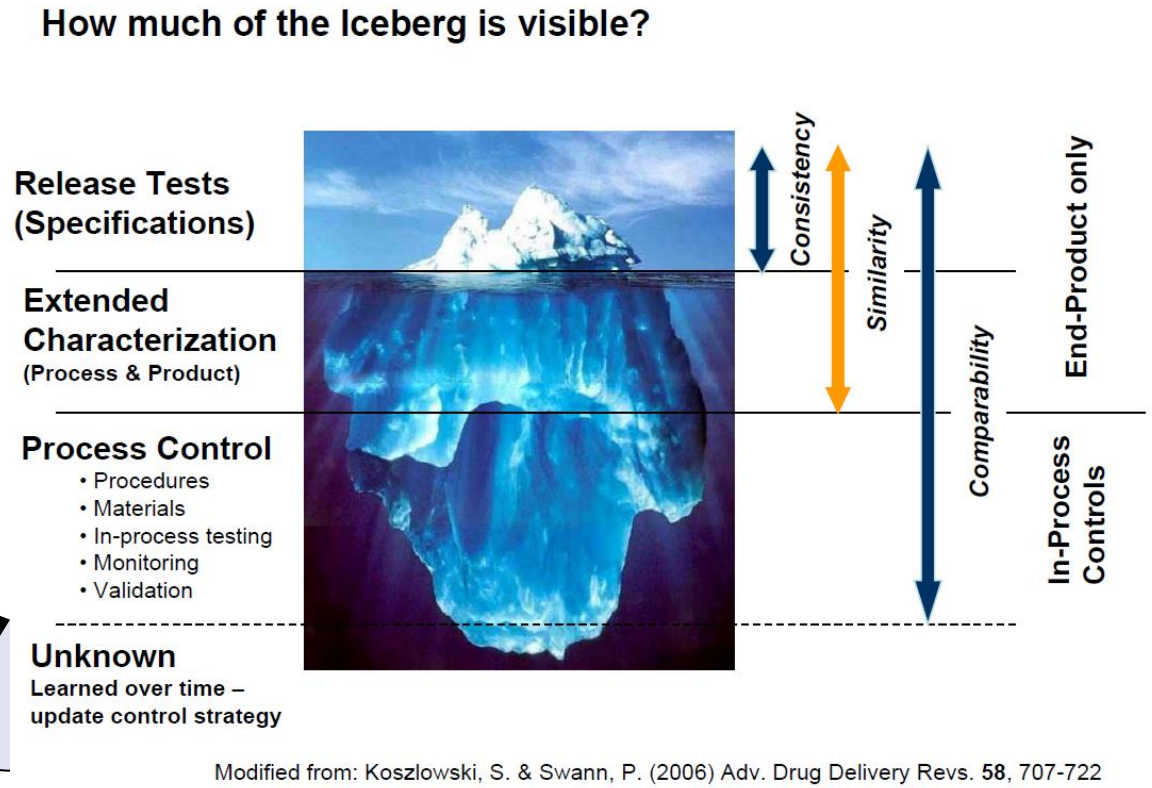
e.g. Subject of :

Monograph

Comparability Exercise

Control Strategy / PQS

Residual Uncertainty



Modified from: Koszlowski, S. & Swann, P. (2006) Adv. Drug Delivery Revs. **58**, 707-722

G.-B. Kresse / CMC

Utility of monographs for biologicals – Regulatory benefits / needs

Regulatory Benefits

- Provide a minimum quality standard (e.g. release tests).
- Provide guidance on limits for certain critical attributes.
- Monographs increase transparency, e.g. versus EPAR.
- Facilitate convergence on robust (validated) methods.

Utility of monographs for biologicals – Regulatory benefits / needs

Regulatory needs

- Biologicals are heterogeneous and flexibility is important.
- Robust methods should be state of art / alternatives possible (monograph should not be a development checklist).
- Avoid including highly process dependent attributes.
- Monograph (and reference standard) - NOT regulatory standards for demonstration of biosimilarity for MAA.

Biosimilars: EMA website landing page

- Authorised Products
- Presubmission / Q&A
- Scientific Advice
- Links to BMWP / guideline

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Biosimilar medicines

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A similar biological or 'biosimilar' medicine is a biological medicine that is similar to another biological medicine that has already been authorised for use. Biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies.

Biosimilars can only be authorised for use once the period of **data exclusivity** on the original 'reference' biological medicine has expired. In general, this means that the biological reference medicine must have been authorised for at least 10 years before a similar biological medicine can be made available by another company.

Role of the European Medicines Agency

The Agency is responsible for **assessing applications** from companies to market **biological medicines** for use in the European Union (EU), including biosimilar medicines.

▸ Biosimilar medicines authorised via the Agency (opens in new window)

Tailored scientific advice pilot project (new)

EMA will launch a tailored scientific advice pilot project in February 2017 to support the development of **new biosimilars**.

The tailored procedure will advise developers on the studies they should conduct, based on a **review of the quality, analytical and functional data** they already have available. Standard scientific advice does not include the assessment of existing data.

The pilot is open to **all types of biosimilars** and includes a pre-submission meeting to review the suitability of the data package. Applicants should note that EMA's Scientific Advice Working Party will need an extra month in addition to normal scientific advice timelines to review applications.

EMA plans to run the pilot until it has completed six scientific advice requests, with maximum one scientific advice request accepted per month. The Agency will analyse the outcome after completing the pilot.

For more information:

▸ Tailored scientific advice to support step-by-step development of new biosimilars

Requirements for authorisation of biosimilar medicines

For biosimilar medicines, the company needs to carry out **studies** to show that the medicine:

- is similar to the reference medicine;
- does not have any meaningful differences from the reference medicine in terms of quality, safety or efficacy.

As information on the reference medicine is already available, the amount of information on safety and efficacy needed to recommend a biosimilar for authorisation is usually less than the amount needed to authorise an original biological medicine.

As with all medicines, the Agency continues to monitor the **safety of biosimilar medicines** once they are on the market.

Documents of interest

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Document(s)	Language	Status	First published	Last updated	Effective Date
Questions and answers on biosimilar medicines (similar biological medicinal products)	EN = English GO		30/10/2008	28/09/2012	
Biosimilar medicinal products	(English only)		29/03/2011	22/05/2013	

Related links

- Scientific guidelines on biosimilar medicines
- Biosimilar Medicinal Products Working Party
- Questions and answers: Similar-biological-product applications

Thank you

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