Comparison of US/EU Biosimilar Guidelines

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Agenda

- Definition of Biosimilarity
- Biosimilar Guidelines Issuance in the EU and US
- Regulation of Biosimilars and FOBs in the US
- Approval Pathways for Drugs/Biologics in the US
- BLA: 351(a) vs 351(k)
- Biosimilars approved in the EU
- Comparison of EU and US guidelines
- US & EU Updates

Definition of Biosimilar/Biosimilarity

- A **similar biological** or '**biosimilar**' medicine is a biological medicine that is similar to another biological medicine that has already been authorised for use and it does not have any meaningful differences from the reference medicine in terms of **quality, safety or efficacy.**

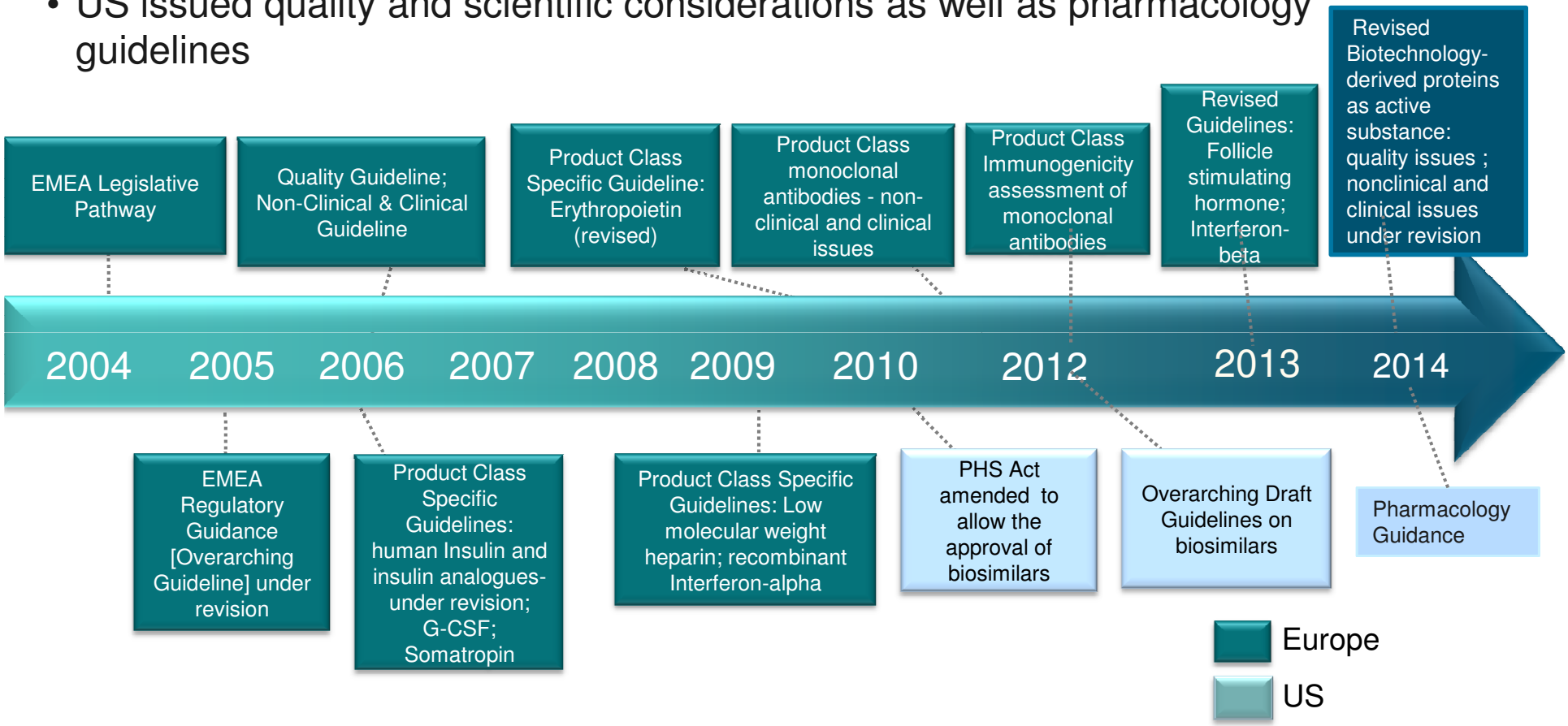
  Article 6 of regulation(EC) No 726/2004 and Article 10(4) of Directive 2001/83, as amended.

- The PHS Act defines *biosimilarity* "to mean that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and… there are no clinically meaningful differences between the biological product and the reference product in terms of the **safety, purity, and potency** of the product."

  Section 7002(b)(2) of the Affordable Care Act, amending section 351(i) of the PHS Act.

Biosimilar Guidelines Issuance in the EU and US

- EU pioneered the development of biosimilar guidelines
- US issued quality and scientific considerations as well as pharmacology guidelines



http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp

US Food and Drug Administration. Guidance for industry. Scientific considerations in demonstrating biosimilarity to a reference product. Draft Guidance. Feb 2012. Pharmacology Guidance 2014

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Regulation of Biosimilars and Follow on Biologics in the US

US Congress amended the Public Health Service Act (PHS 351) to allow for the approval of biosimilars in the US and President Obama signed the "Patient Protection and Affordable Care Act" into law on March 22, 2010.

- **FDA Authority:** The new law provides FDA the latitude to forego some of the nonclinical and clinical requirements, if, in its opinion, such requirements are unnecessary.

- FDA's Premise on 505 (b)(2) under Federal FD&C Act: can approve a therapeutic protein product that is sufficiently similar to a licensed reference product.

- Follow on biologics previously approved by the FDA pursuant to Federal FD&C Act:
  - **Omnitrope** (somatropin), a growth hormone; reference product Genotropin® - 505(b)(2) - 2006
  - **Valtropin** (somatropin), a growth hormone; reference product Humatrope® - 505(b)(2) - 2007
  - **Hylenex** ((Hyaluronidase), family of enzymes that degrade hyaluronic acid to increase tissue permeability; reference product Wydase- 505(b)(2) – 2005
  - **Fortical** (Calcitonin Salmon), acts to reduce blood calcium (for osteoporosis);reference product Miacalcin- 505(b)(2) – 2005
  - **Basaglar** (insulin glargine), tentative approval for insulin for type 2 diabetes; reference product Lantus-505(b)(2) -2014 (currently under litigation)

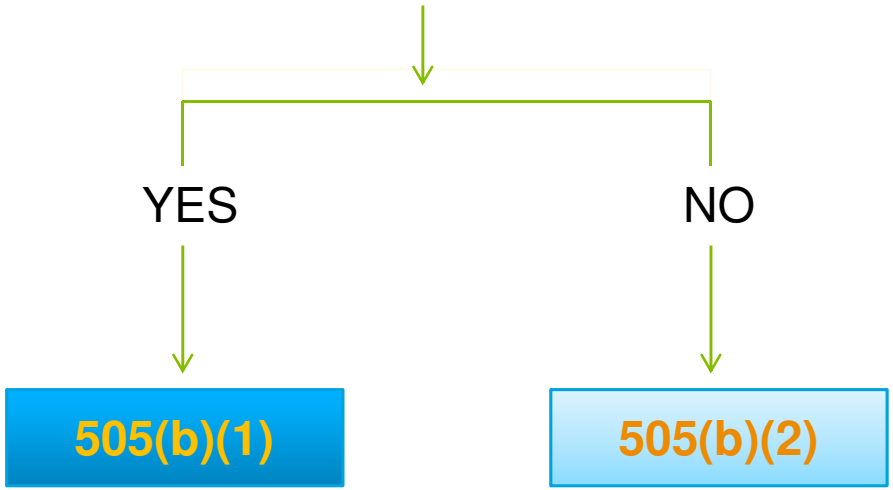
Source: FDA website, available at . http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm

Approval Pathways for Drugs/Biologics in the US

FFD&C Act

New Drug Applications (NDAs)

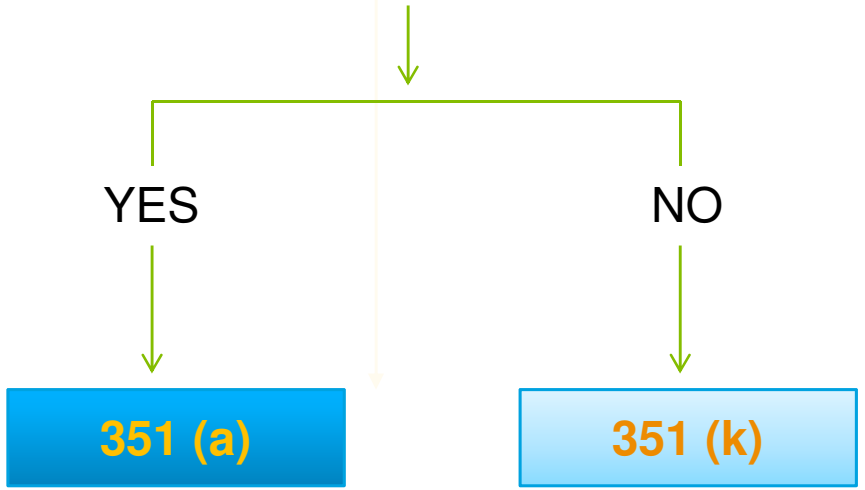
- *"Full Reports" of Safety and Efficacy Investigations*
- *Applicant has right of reference to essential investigations*



PHS Act

Biologic License Applications (BLAs)

- *Full Reports" of Safety and Efficacy Investigations*
- *Applicant has right of reference to essential investigations*



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EMA has approved 18 biosimilars for 7 originator products

INN	Originator (Company)	Biosimilar	Company	Approval
Somatropin	Genotropin® (Pfizer)	Omnitrope	Sandoz	Apr-06
	Humatrope® (Lilly)	(Valtropin*)	Biopartners	Apr-06
		Somatropin Biopartners	Biopartners	Aug-13
Epoetin α	Eprex® (J&J)	Binocrit/Epoetin Alfa Hexal	Sandoz (Hexal)	Aug-07
		Abseamed	Medice	Aug-07
Epoetin ζ	Eprex® (J&J)	Retacrit	Hospira	Dec-07
		Silapo	Stada	Dec-07
Filgrastim	Neupogen® (Amgen)	Ratiograstim/(Filgrastim Ratiopharm*)	Ratiopharm	Sep-08
		Tevagrastim	Teva	Sep-08
		Biograstim	CT Arzneimittel	Sep-08
		Zarzio/Filgrastim Hexal	Sandoz (Hexal)	Feb-09
		Nivestim	Hospira	Jun-10
		Grastofil	Apotex	Oct-13

**Withdrawn*

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EMA has approved 18 biosimilars for 7 originator products (continued)

INN	Originator (Company)	Biosimilar	Company	Approval
Infliximab	Remicade® (J&J)	Inflectra	Hospira	Sep-13
		Remsima	Celltrion	Sep-13
Follitropin α	Gonal-F® (Merck)	Ovaleap	Teva	Sep-13
		Bemfola	Finox Biotech	Mar-14
Insulin glargine	Lantus® (Sanofi)	Abasria	Eli Lilly/Boehringer Ingelheim	Sep-14

Since 2006, experience with biosimilars in Europe has not revealed any unusual or unexpected adverse events compared with originator biologics[1,2]

1. Ebbers *et al.* 2012; 2. McCamish & Woollett 2012

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EU/US Guidances - A comparison

Essential Components	EU EMA	US FDA
Reference product against which the biosimilar is compared must be licensed and sourced in their jurisdiction	✓	✓
Dosage form, strength and route of administration should be the same as the reference product	✓	✓
The reference product must be licensed based on full quality, safety an efficacy data (full dossier)	✓	✓
Same reference product should be used throughout development	✓	✓
Facility/facilities producing active ingredient and biosimilar product must meet cGMP guidelines	✓	✓
A formulation can have minor differences in clinically inactive ingredients as long as they do not result in clinically meaningful differences	✓	✓

EU/US Guidances - A comparison

Essential Components	EU EMA	US FDA
Stepwise development: Each step of the development must demonstrate acceptable similarity before proceeding to the next step: CMC → Non-Clinical → Clinical	✓	✓
The expression construct for the biosimilar product will "encode the same primary amino acid sequence" as the licensed reference product	✓	✓
Analytical and functional characterization – head to head similarity with licensed reference product	✓	✓
Stepwise approach for the clinical development – demonstrate similarity in PK/PD studies prior to conducting Phase III study or studies	✓	✓
Clinical Phase I PK/PD (if relevant PD marker is available) study. Immunogenicity assessment required.	✓	✓
Clinical Phase III study to assess safety and efficacy. Immunogenicity assessment required.	✓	✓

EU/US Guidances - A comparison

Essential Components	EU EMA	US FDA
Risk-based approach – biosimilar products will be approved based on "totality of the evidence" – even a relatively small difference in e.g. clinical efficacy may not be accepted if the analytical and nonclinical data indicate important structural and functional differences	✓	✓
Biosimilar Application: must show that the indications for which the biosimilar product applicant is seeking approval have been previously approved for the reference product	✓	✓
Extrapolation of Indication(s) allowed, if the MOA is the same for all approved indications for the reference product. In some cases additional PK data in patient population may be required.	✓	✓

EU/US Guidances - A Comparison

Essential components	EU EMA	US FDA
Interchangeability: defined as a "biological product [that] may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product"****	***	✓****
Immunogenicity testing	6+months	6+ months
Transition study	Not required	✓
Pediatric Study Assessment	No	✓*****
Pharmacovigilance plan	✓	✓

***Not centrally determined. Decision is left to each member state

**** Data provided to show that switching between use of the biosimilar product and the reference product is as safe as using only the reference product

***** yes, if product is found to be biosimilar. No, if product is found to be interchangeable.

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EU/US Guidances - A Comparison

Additional Aspects	EU EMA	US FDA
A proposed biosimilar product can be licensed for fewer than all indications licensed for the reference product	✓	✓
A proposed biosimilar product can have delivery device or container closure system that is different from reference product	✓	✓
A proposed biosimilar product can seek licensure for fewer than all presentations for which a reference product is licensed	✓	✓
A proposed biosimilar product can seek licensure for fewer than all routes of administration for which a reference product is licensed	✓	✓
Joint Scientific Advice available from FDA/EMA	✓	✓

EU/US Guidances - A Comparison

Additional Aspects	EU EMA	US FDA
Exclusivity period for an innovator biologic	8+2+1 years	12 years
Exclusivity period for the first interchangeable product	--	12 months
Differences that could have an advantage as regards to safety (e.g., lower levels of impurities or lower immunogenicity) may not preclude biosimilarity.	✓	✓
Excludes 'intended changes to improve efficacy' from scope of biosimilarity approach.	✓	✓

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US & EU Updates

US

- Late 2012, BsUFA became effective, now other than Biosimilar Initial Advisory meeting with the FDA, there is an annual fee for Type 1 to Type 4 meetings
- Pharmacology Draft Guidance published in 2014
- As of third quarter 2014, FDA received 78 requests for initial meetings to discuss biosimilar development programs
- Meetings pertained to 14 different reference products
- The agency has held 63+ initial meetings with sponsors
- Received 28 IND applications for biosimilars

EU

- Since 2012, EMA posts on its website on monthly basis as to dossiers submitted by type of product (insulin, infliximab, etc.)
- First monoclonal biosimilar approved in 2013
- Revisions to some guidances based on experience to date

Thank you very much!!

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