EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Biosimilars: the EU regulators' view

Seminario "Farmaci biosimilari e antitrust"

Presented by Stefano Marino on 30 May 2017
Head of Legal Department - European Medicines Agency

# Similar Biological Medicinal Products (biosimilars) – *so far…*

- Over 10 years experience with biosimilars in the EU confirms their safe and effective use
- Rapid advances in the analytical sciences allow comprehensive characterisation of increasingly complex molecules and optimisation of data requirements ⇒ increased interest in the biosimilar market
- Approval based on demonstrating no clinically meaningful differences compared with the reference medicine by extensive comparison of quality, non-clinical and clinical data with the reference medicinal product

# Currently **28 biosimilars** approved through the Centralised Procedure

| Medicine Name | Active Substance | Authorisation dat |
|---|---|---|
| Abasaglar (previously Abasria) | insulin glargine | 09/09/2014 |
| Abseamed | epoetin alfa | 28/08/2007 |
| Accofil | filgrastim | 18/09/2014 |
| Amgevita | adalimumab | 22/03/2017 |
| Bemfola | follitropin alfa | 27/03/2014 |
| Benepali | etanercept | 14/01/2016 |
| Binocrit | epoetin alfa | 28/08/2007 |
| Epoetin Alfa Hexal | epoetin alfa | 28/08/2007 |
| Filgrastim Hexal | filgrastim | 06/02/2009 |
| Flixabi | infliximab | 26/05/2016 |
| Grastofil | filgrastim | 18/10/2013 |
| Inflectra | infliximab | 10/09/2013 |
| Inhixa | enoxaparin sodium | 15/09/2016 |
| Lusduna | insulin glargine | 04/01/2017 |
| Movymia | teriparatide | 11/01/2017 |
| Nivestim | filgrastim | 08/06/2010 |
| Omnitrope | somatropin | 12/04/2006 |
| Ovaleap | follitropin alfa | 27/09/2013 |
| Ratiograstim | filgrastim | 15/09/2008 |
| Remsima | infliximab | 10/09/2013 |
| Retacrit | epoetin zeta | 18/12/2007 |
| Silapo | epoetin zeta | 18/12/2007 |
| Solymbic | adalimumab | 22/03/2017 |
| Terrosa | teriparatide | 04/01/2017 |
| Tevagrastim | filgrastim | 15/09/2008 |
| Thorinane | enoxaparin sodium | 15/09/2016 |
| Truxima | rituximab | 17/02/2017 |
| Zarzio | filgrastim | 06/02/2009 |

*Data from EMA website, consulted on May 2017*

# Defined Legal Basis – Article 10(4) of Directive 2001/83/EC

## Similar Biological Medicinal Product

"*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.*

*The **type and quantity of supplementary data** to be provided must comply with the relevant criteria stated in **Annex I** and the **related detailed guidelines**. The results of other tests and trials from the reference medicinal product's dossier shall not be provided."*

Mandatory under the centralised procedure if developed by means of biotechnological processes, as provided by Article 3(1) of Regulation (EC) No 726/2004, *however optional scope also possible*

# Applicable Definitions

**Biological medicinal product:** a product, the active substance of which is a biological substance, i.e. substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control

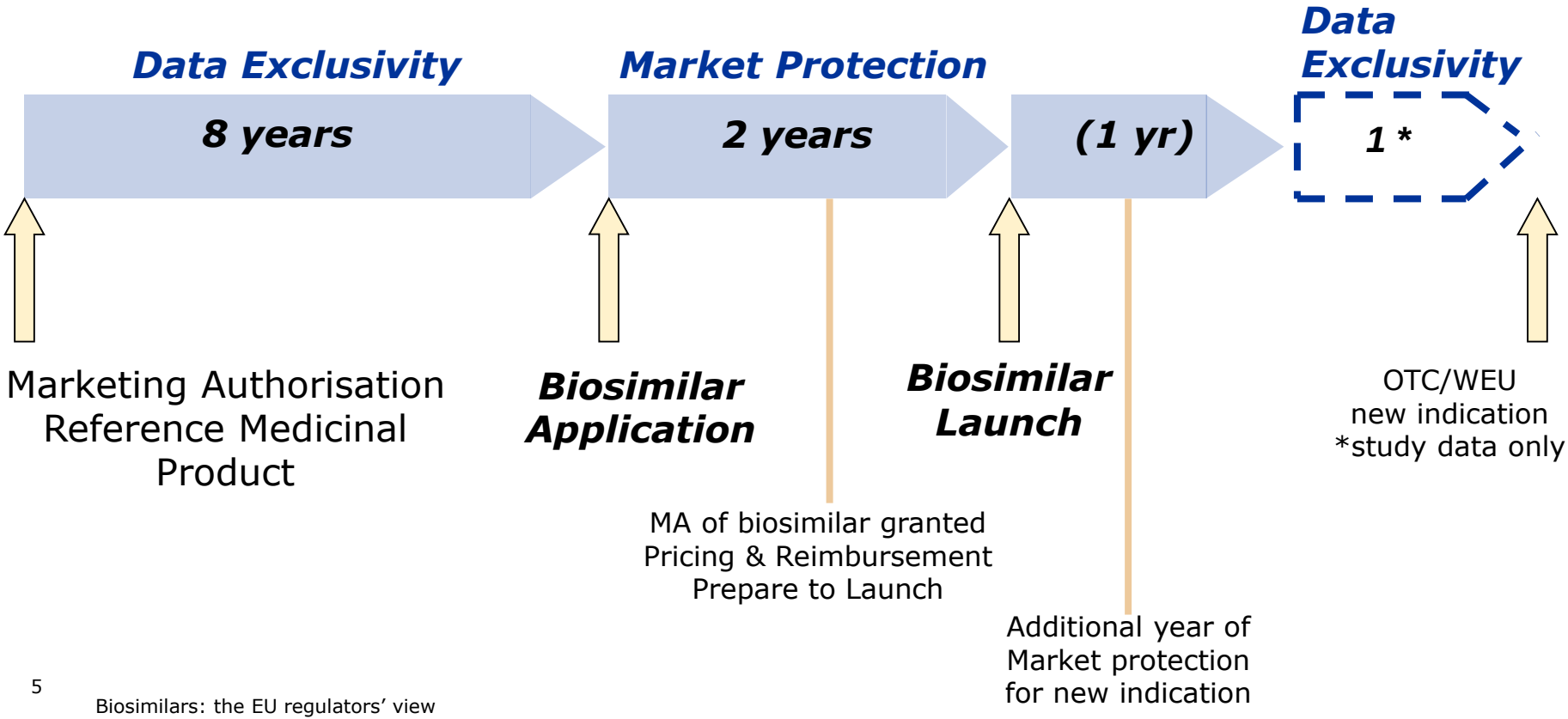
**Reference medicinal product**: a medicinal product authorised under Article 6, in accordance with the provisions of Article 8 of Directive 2001/83/EC

**Data exclusivity/data protection**: period of time during which a company cannot cross-refer to the data in support of another marketing authorisation

**Market protection**: period of time during which a generic, hybrid or biosimilar cannot be placed on the market

**Market exclusivity**: period of time during which a medicinal product which is similar to an orphan medicinal product cannot be validated by the EMA (applicable to all legal basis)

# Protection Periods



# **Data exclusivity** and **Global Marketing Authorisation**

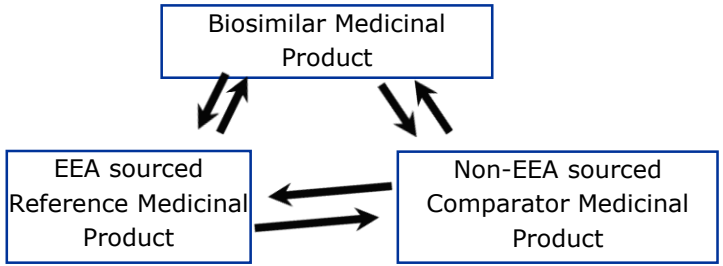
Article 6(1) 2nd paragraph of Directive 2001/83/EC states:

"*When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1).*"

All variations and extensions to a marketing authorisation, including additional strengths, pharmaceutical forms, administration routes or presentations **shall be considered as part of the same marketing authorisation for the purposes of applying the rules on data exclusivity**

# Choice of Reference Medicinal Product

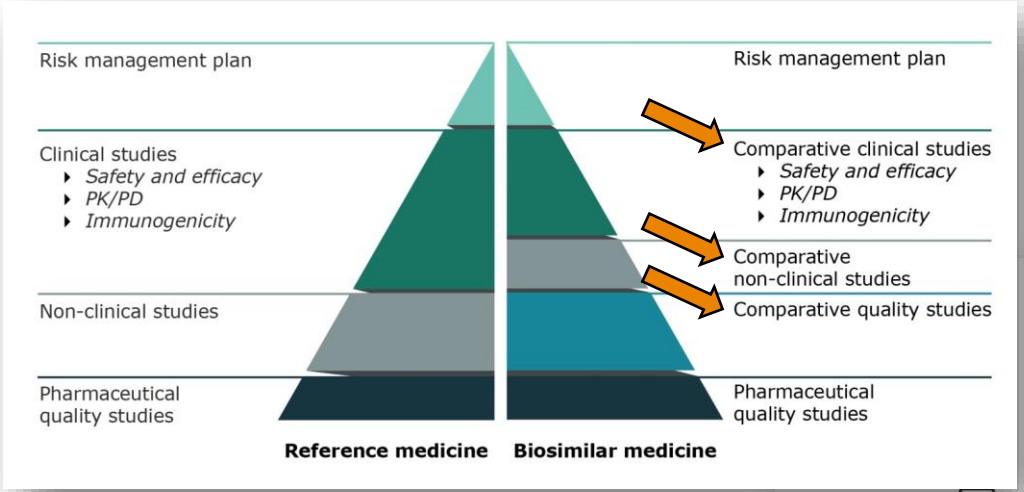
- Reference medicinal product must be **authorised in the EEA** as provided by Article 10(2)(a) of Directive 2001/83/EC
- However, to **facilitate global development of biosimilars** and **avoid unnecessary repetition of clinical trials**, it may be possible to compare the biosimilar in certain clinical studies and in *in vivo* non-clinical studies (where needed) with a comparator authorised by a **non-EEA regulatory authority** with similar scientific and regulatory standards as EMA (e.g. ICH countries): "*We will accept that a biosimilar application contains clinical data with reference products that are not sourced from the EU*" (Commissioner John Dalli, *Health and Consumer Policy*, participation at 18th EGA Annual Conference (15 June 2012)[1]





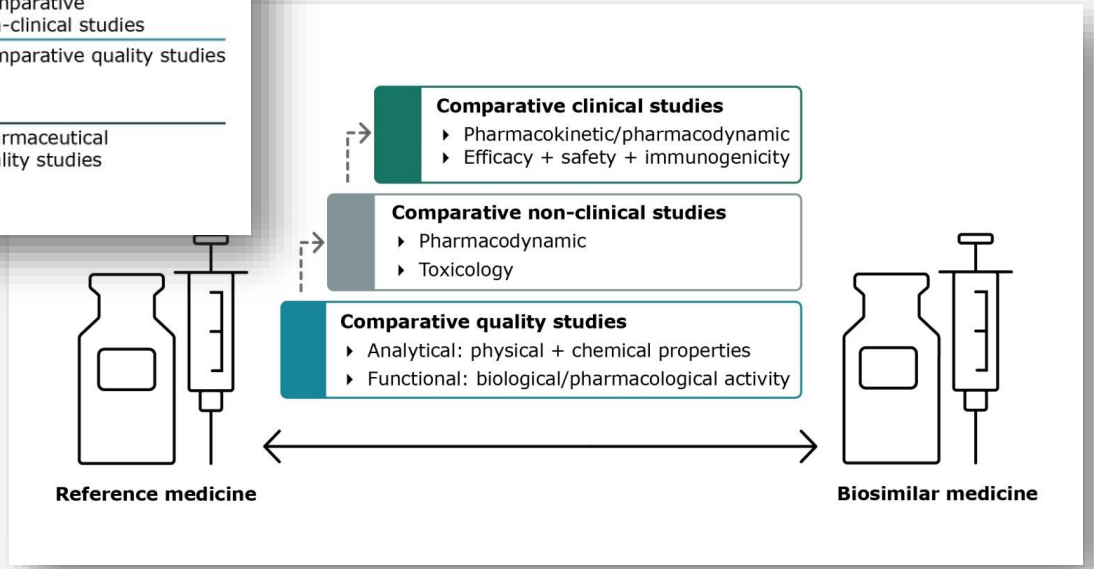

[1] – Available at: http://ec.europa.eu/archives/commission_2010-2014/dalli/docs/speech_15062012.pdf

# Biosimilars Development – main concepts

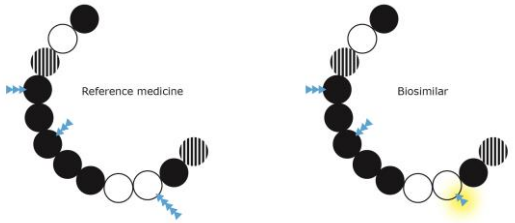



*Data submission*

*Stepwise approach*



# Specific Features of biosimilar medicines




- Highly similar to the reference medicine

  The biosimilar has physical, chemical and biological properties very similar to the reference medicine. There may be minor differences from the reference medicine which are not clinically meaningful in terms of safety or efficacy.

- No clinically meaningful differences compared with the reference medicine
- Batch variability of biosimilar and reference medicine kept within strict limits
- Same strict standards of quality, safety and efficacy

# Extrapolation of indications – *supported by comparative data submitted*

Criteria for extrapolation

- *Mechanism of action*
- *Relevant study population*
- *Extrapolation across different clinical settings*
- *Extrapolation of safety data*
- *Extrapolation of immunogenicity data*

*Extrapolation is not a new concept but a well-established scientific principle used routinely when biological medicines with several approved indications undergo major changes to their manufacturing process.*

*The scientific criteria for extrapolation of efficacy and safety data are supported by over 10 years experience of safe and effective use of biosimilars in the EU.*

# Interchangeability, switching and substitution (1)


Prescribing practices and advice to prescribers fall under the **responsibility of EU Member States**, which have the necessary legal framework in place and may issue regulations, guidelines and advice in their areas of competence

**Interchangeability**: possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect, i.e. replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another:

- **Switching**, which is when the prescriber decides to exchange one medicine for another medicine
- **Substitution** (automatic), which is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber

*Source: EMA and EC Information guide for healthcare professionals on biosimilar medicines, 2017*

# Interchangeability, switching and substitution (2)

From a scientific perspective,

"*There is also* ***no reason to believe that harmful immunogenicity should be expected after switching between highly similar biological medicines***"

EMA and EC Information Guide to HCP, published 5 May 2017,

*http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf*

# Data included in the SmPC and EPARs for biosimilars

- Section 5.1 (pharmacodynamic properties) of the SmPC will identify a medicine as a biosimilar with the following wording:

  *[Brand name] is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.*

- **A biosimilar can be approved for some or all of the authorised indications of the reference medicinal product –** due to applicant's market strategy (including patent concerns) or clinical data submitted

- Healthcare professionals should confirm that the biosimilar is authorised for the intended indication

- EPARs detail the development and comparability studies to demonstrate biosimilarity, and where applicable scientific rational for extrapolation of data

# Biosimilars – concluding remarks

- The EU has so far the highest number of biosimilar medicines approved worldwide - it gained over the years an extensive experience in this field
- A specific legal basis on biosimilars has been in place in the EU since 2004
- If the product is manufactured by a biotechnological process, EMA is exclusively competent for its assessment (Annex to Regulation (EC) No 726/2004, as provided in Article 3(1))
- A generic of a biological product may be applied for under Article 10(1) of Directive 2001/83/EC
- EMA does not regulate switching/substitution of a reference medicine by its biosimilar - this falls within the remit of EU Member States
- To our knowledge there are no pending Court cases involving EMA or the Commission on biosimilars. A previous case (Case T-15/04 *Sandoz GmbH v EC*) was withdrawn on 13 July 2006

# Thank you for your attention

## Further information

Biosimilar medicines: marketing authorisation - EMA webpage

**European Medicines Agency**
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

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