EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Biosimilars – EMA approval process

ACG 2017: FDA-EMA workshop on biosimilars

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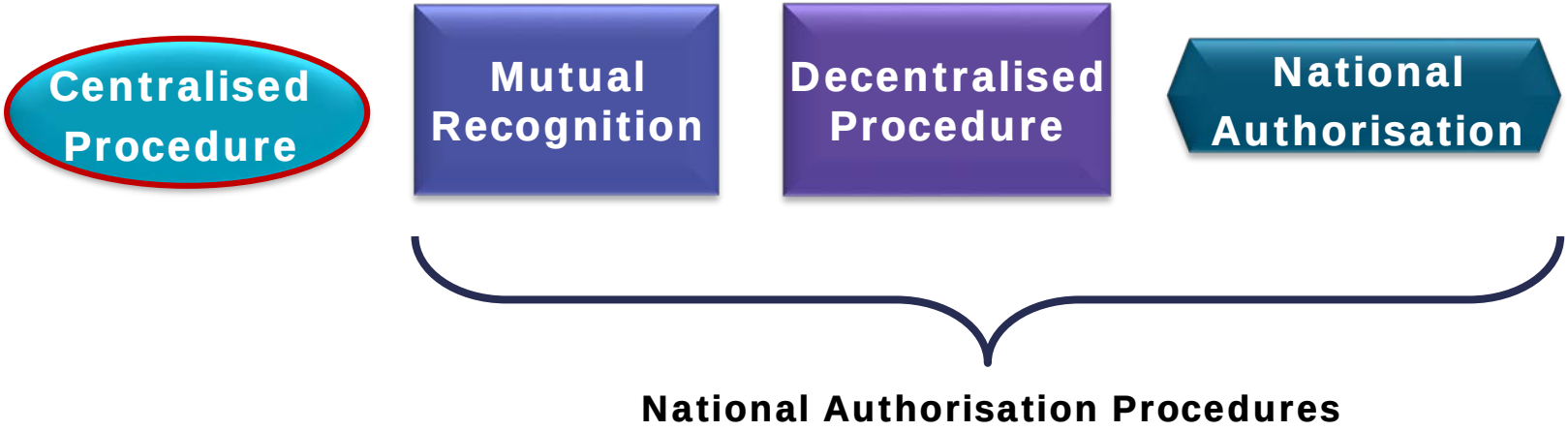
An agency of the European Union

The European System

Marketing authorisation: allows a medicine to be placed on the market for sale and supply

Two ways of obtaining a marketing authorisation: Centralised procedure and National Authorisation procedures



Medicines that are mandatory for evaluation at EMA

- Rare diseases
- HIV, cancer, neurodegenerative disorders, diabetes
- Auto-immune diseases, viral diseases
- All biotech products
- Gene therapy
- Monoclonal antibodies

± Other innovative products

The centralised procedure and the EMA

ONE

⇒ Marketing Authorisation application

⇒ Evaluation

⇘

- Authorisation in all EU MS
- Invented name
- Product information

- Summary of Product Characteristics (SmPC)
- Labelling
- Package Leaflet (PL)

⇒ **ALL** EU languages

The 7 Committees:

CHMP

Committee for Human Medicinal Products

PRAC

Pharmacovigilance Risk Assessment Committee

COMP

Committee for Orphan Medicinal Products

PDCO

Paediatric Committee

CAT

Committee for Advanced Therapies

CVMP

Committee for Veterinary Medicinal Products

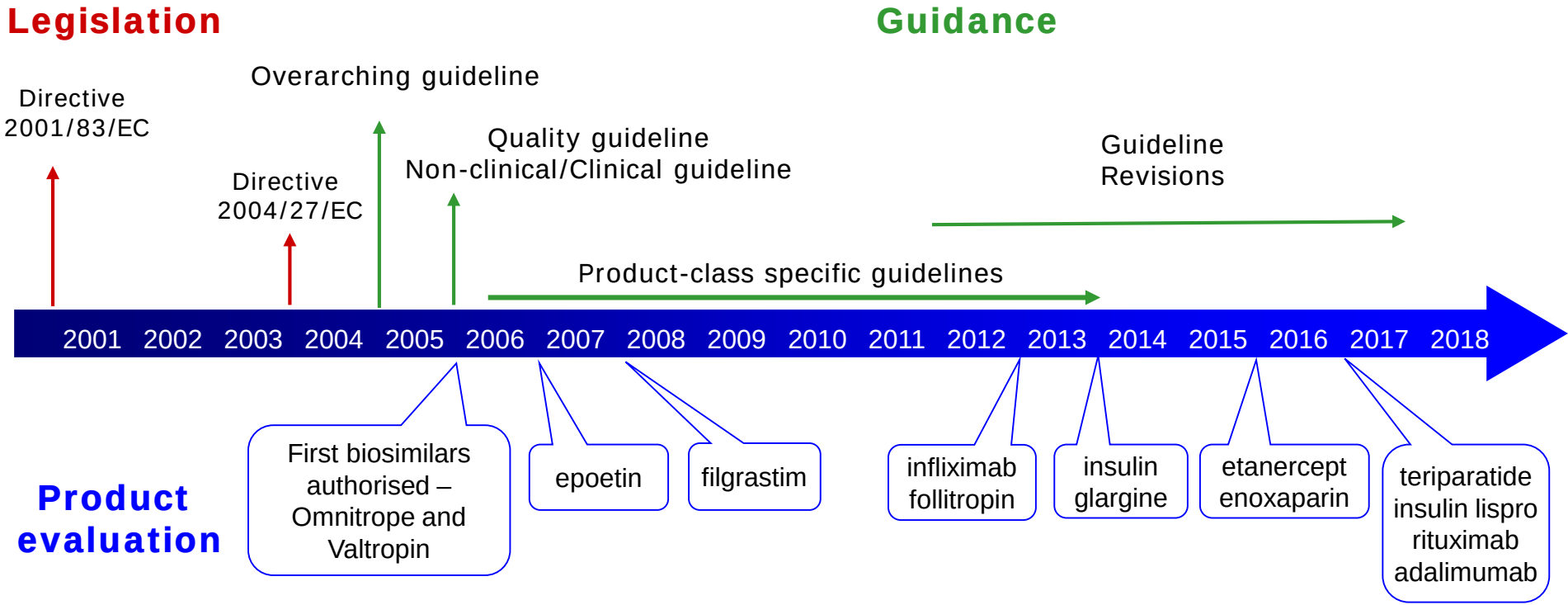
HMPC

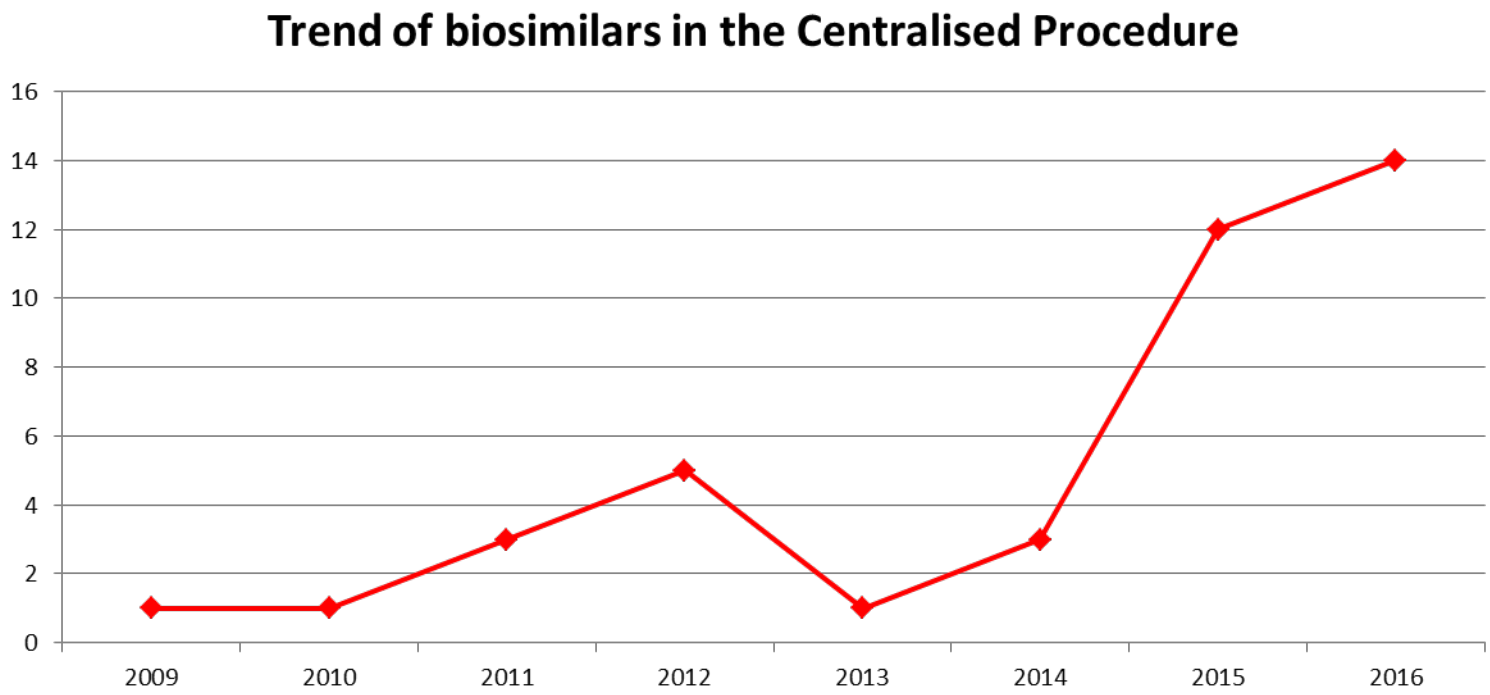
Committee for Herbal Medicinal Products

System of Rapporteurs

Committee Plenary Meeting

Evolution of Biosimilars in the EU




Trend of biosimilars in the Centralised Procedure
16
14
12
10
8
6
4
2
0
2009
2010
2011
2012
2013
2014
2015
2016

EU Guidelines for biosimilars

General Guidelines:

Overarching Guideline (CHMP/437/04 Rev. 1)
"Guideline on Similar Biological Medicinal Products"
Revised 2014

Non-clinical/clinical Guideline
Revised 2015

Quality Guideline
Revised 2014

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

Insulin	Somatropin	G-CSF	Epoetin	IFN-α	LMWH	mAbs	IFN-β	Follitropin
2006 Rev. 2015	2006	2006	2006 Rev. 2010	2009	2009	2012	2013	2013
		Revision ongoing		Revision ongoing				

What is a biosimilar?

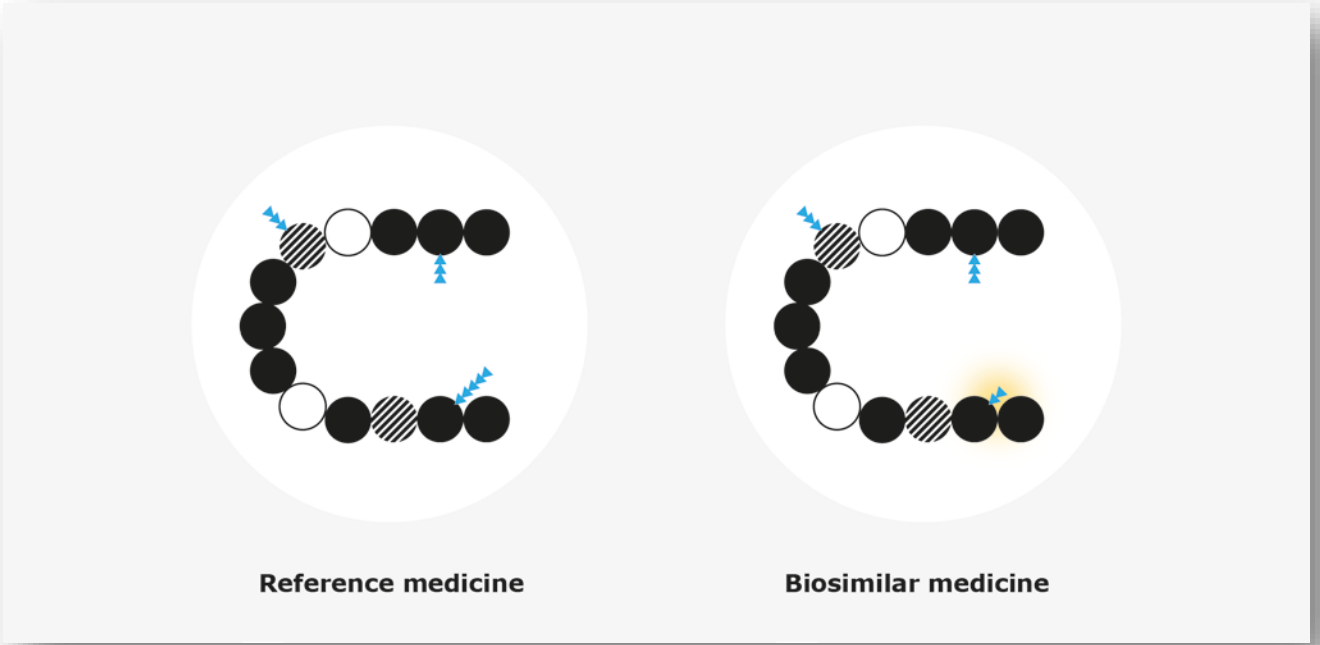
Directive 2001/83/EC, Article 10(4):

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 the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.

“Overarching ” biosimilar guideline:

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.

Graphics to address a key question: how similar is a biosimilar?



Stepwise approach for demonstration of biosimilarity

- The manufacturer of the biosimilar will not have access to the manufacturing process of the originator and its therefore impossible to produce an “identical” product
- Stepwise head to head comparison is needed to demonstrate that the biosimilar and reference product have highly similar profiles in terms of quality, safety and efficacy

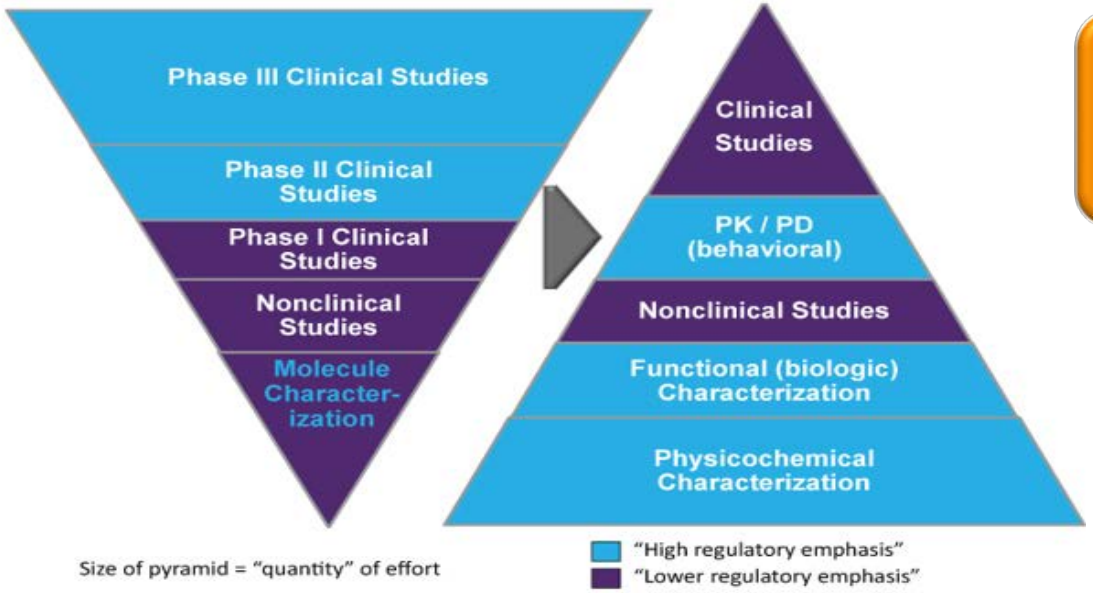
There should be no **clinically meaningful differences** between the two products

Tables to allow for more detailed information

Table 4. Overview of biosimilar development compared with a reference medicine

Biological medicine with new active substance (e.g. reference medicine)	Biosimilar medicine
No previous knowledge of safety and efficacy	Builds on knowledge of safety and efficacy from years of clinical use with reference medicine
Development aims at demonstrating safety and efficacy directly in patients	Development aims at demonstrating comparable safety and efficacy by establishing biosimilarity
Comparability studies only for manufacturing changes during development (e.g. producing larger batches for clinical trials)	Comprehensive comparability studies with the reference medicine

Biosimilarity is based on the “totality of evidence”



Demonstration of biosimilarity follows some of the principles of comparability testing (ICH Q5E) for pre- and post-change manufacturing process

Physiochemical and functional assays are the most sensitive to reveal subtle differences

Highlighting key messages

Approval of biosimilars builds on existing scientific knowledge on safety and efficacy of the reference medicine gained during its clinical use, so fewer clinical data are needed.

From a scientific and regulatory point of view, the reference medicine's entire clinical development programme does not need to be repeated. This means that patients and healthy volunteers will not be subjected to unnecessary clinical trials.

made by biotechnology[3, 4, 5]. Companies producing biological medicines are likely to adapt or improve the manufacturing process several times during the commercial life of a product (e.g. by increasing production scale). Comparing batches before and after a manufacturing change ensures consistency, so that there are no changes in safety or efficacy.

A change to the manufacturing process must always be approved by regulators. The extent of the comparability studies required following a manufacturing change to a biological medicine will depend on the expected impact on quality, safety and efficacy of the medicine. Most often, analytical and functional data are sufficient, and clinical trials to prove safety and efficacy are not needed (table 5, scenario 1 and 2). Clinical trials are needed only

Extrapolation of efficacy and safety from one therapeutic indication to another

Guideline on Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues

When biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable, but needs to be scientifically justified. In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data will be required. Extrapolation should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data. It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physico-chemical and structural analyses as well as by in vitro functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication

Additional data are required in certain situations, such as

1. the active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indications

2. the active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications

3. the studied therapeutic indication is not relevant for the others in terms of efficacy or safety, i.e. is not sensitive for differences in all relevant aspects of efficacy and safety.

Remsima / Inflectra 1st Biosimilar authorised in IBD

- Physicochemical / functional similarity in more than 50 tests

Only difference between CT-P13 and Remicade Differences in fucosylation impacting upon binding to the Fc receptor FcγRIII in vitro not clinically relevant

- Clinical biosimilarity shown in studies in ankylosing spondylarthritis and active rheumatoid arthritis
- Based on the “totality of the evidence” EMA granted marketing authorisation in 2013

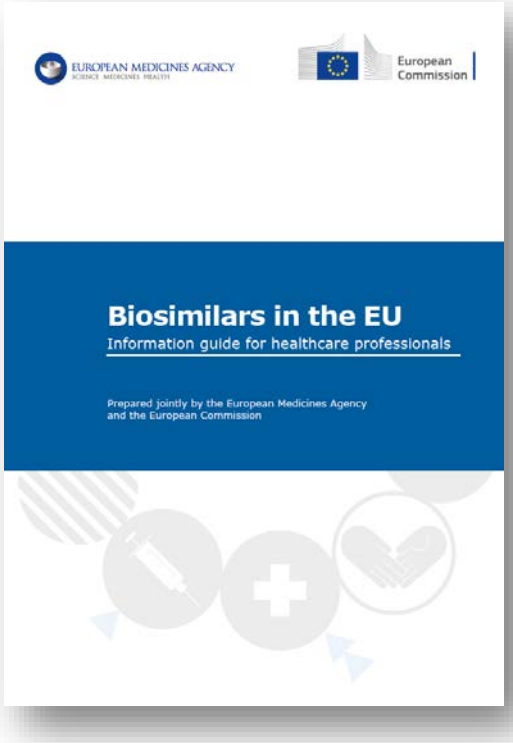
However: Initial concerns of clinicians after Remsima authorisation (absence of IBD data)

Reference information on biosimilars

To foster:

- **Understanding of biological medicines**, including complex nature and manufacturing process
- Sound and common understanding of what **biosimilars** are and how they are **developed and approved in the EU**
- **Confidence** in the use of biosimilars, **as for all medicines** approved by EC
- **Consistency in public health messages** on biosimilars across the EU
- **Trust** in the **robustness of the regulatory system** for approval of biosimilars
- Appreciation of the **safety and efficacy** of biosimilars
- Ability of health professionals to adequately **respond to patients queries** on biosimilars

HCP Information guide on Biosimilars



Target audience:

Healthcare professionals – patients' first point of contact

- Hospital and community pharmacists
- Specialists, General practitioners
- Specialised nurses
- Learned societies

Interchangeability

- The EMA carries out the scientific review of a biosimilar, the evaluations do not include recommendations on whether a biosimilar is interchangable with the reference medicine (switch or substitution)
- Decision on interchangeable use and substitution of the reference medicinal product is taken at national level (prescribing practices and advice to prescribers)

However:

- Several cohort studies across Europe have evaluated clinical efficacy, safety and immunogenicity in patients who were switched from originator to CT-P13 AND The NOR-Switch trial on patients with immune mediated diseases found no differences in terms of clinical response, maintenance of remission, or adverse events in patients receiving CT-P13 compared with those receiving originator infliximab."

Biosimilars authorised for IBD in the EU

Adalimumab

Amgevita: Authorised 22/03/2017

Sylombic: Authorised 22/03/2017

Imraldi: Authorised 24/08/2017

Infliximab

Inflectra: Authorised 10/09/2013

Remsima: Authorised 10/09/2013

Flixabi: Authorised 26/05/2016

Thank you for your attention

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