

# ACG Public Forum

Join ACG, the FDA, and EMA  
for a discussion on biosimilars and IBD

**Monday, 12:45 pm – 2:15 pm**



WCOG@ACG2017  
October 13-18  
Orlando, Florida



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Biosimilars – EMA approval process

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ACG 2017: FDA-EMA workshop on biosimilars

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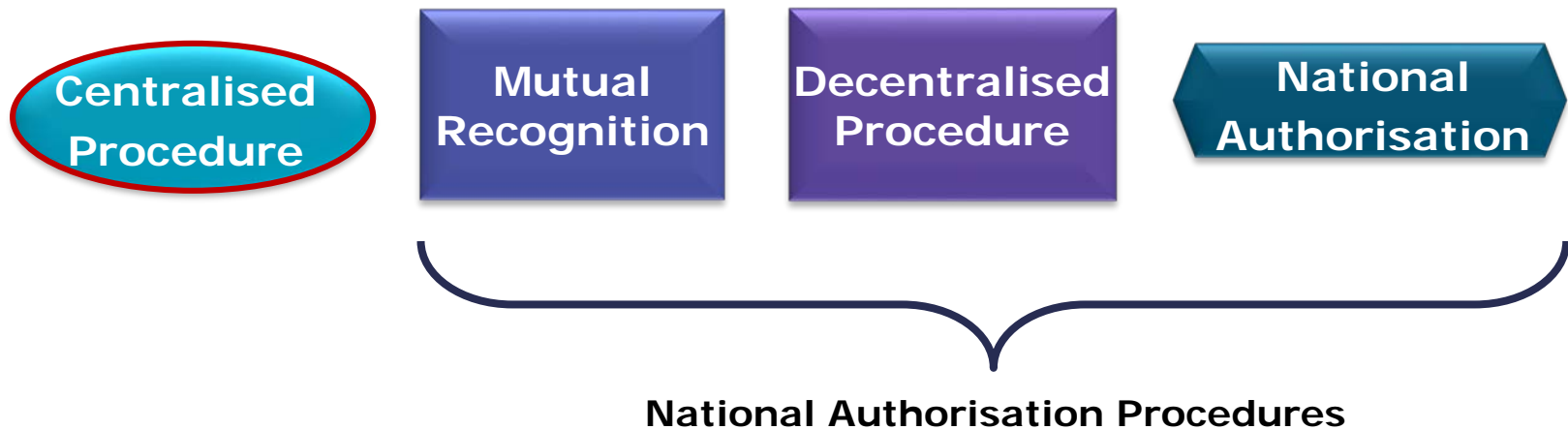
An agency of the European Union



# 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



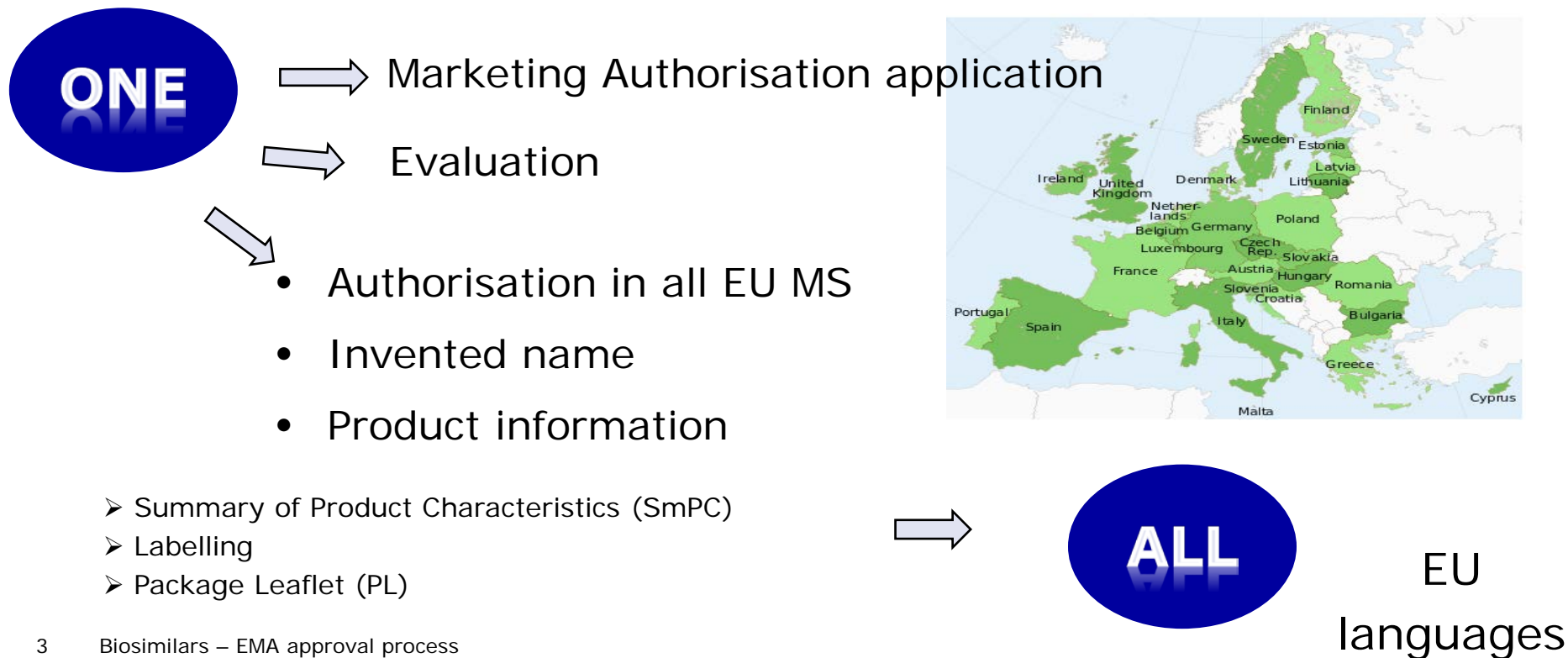


## Medicines that are mandatory for evaluation at EMA

- 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





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

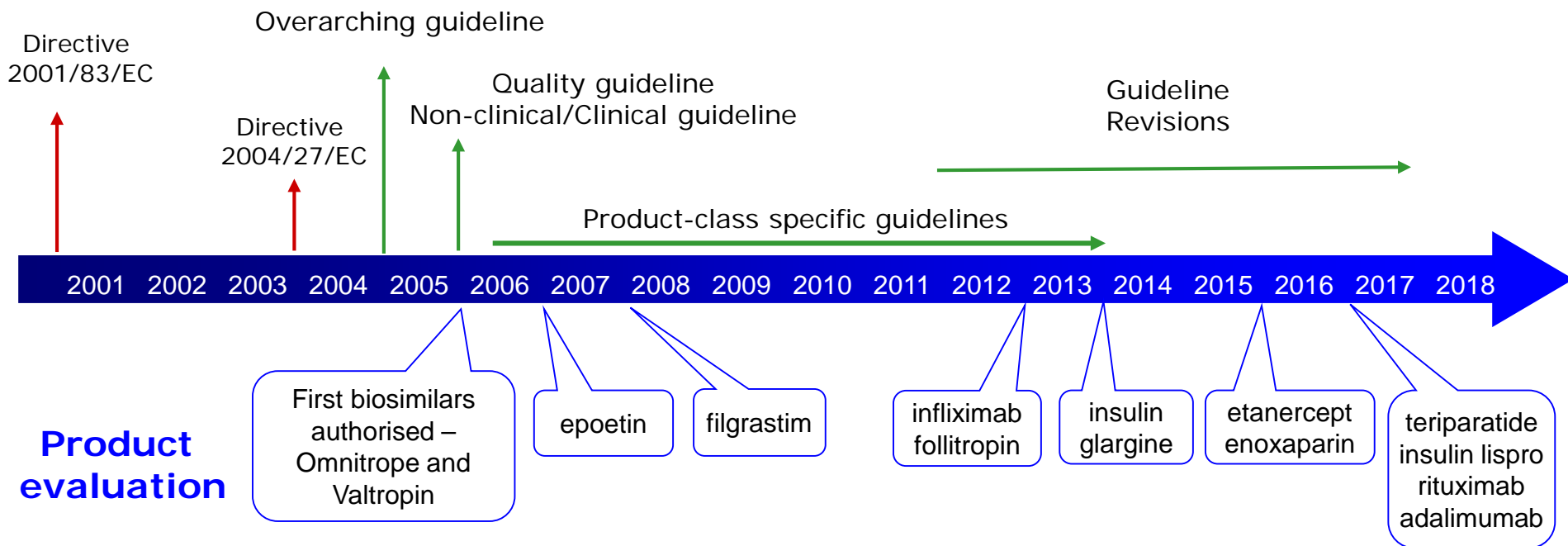




# Evolution of Biosimilars in the EU

## Legislation

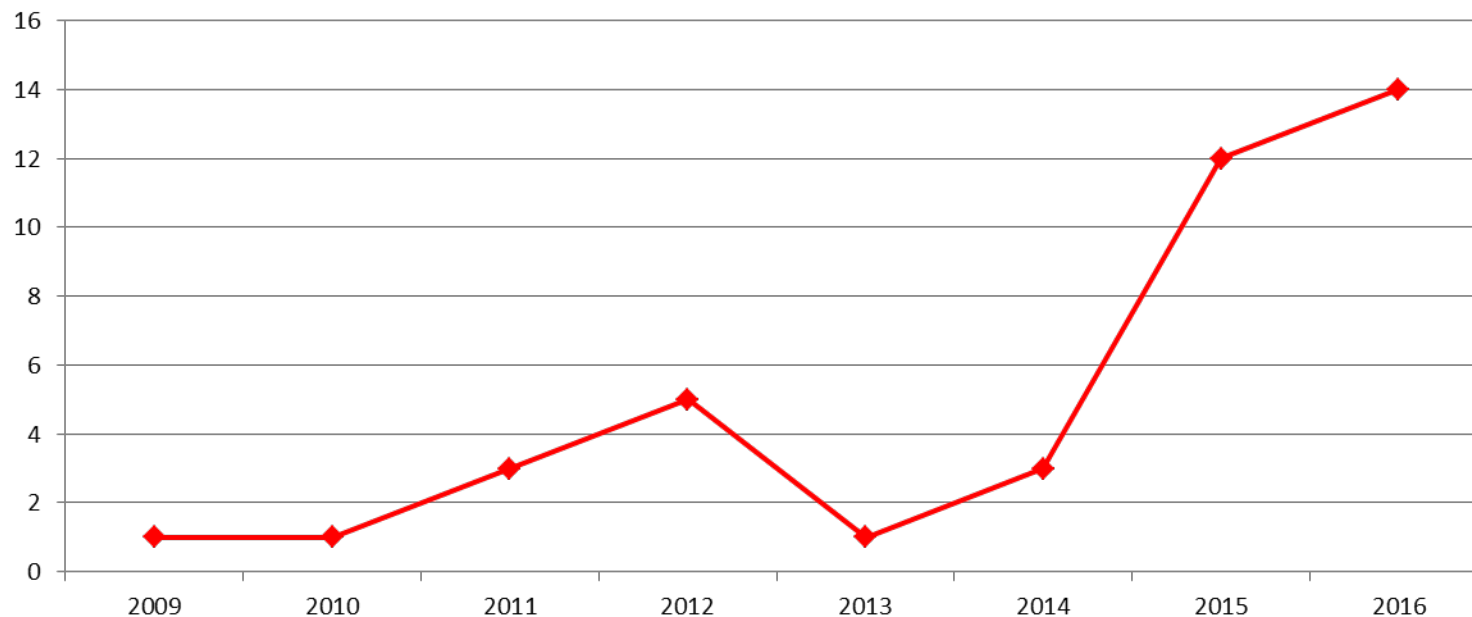
## Guidance







## Trend of biosimilars in the Centralised Procedure



# EU Guidelines for biosimilars

## General Guidelines:

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

Revised  
2014

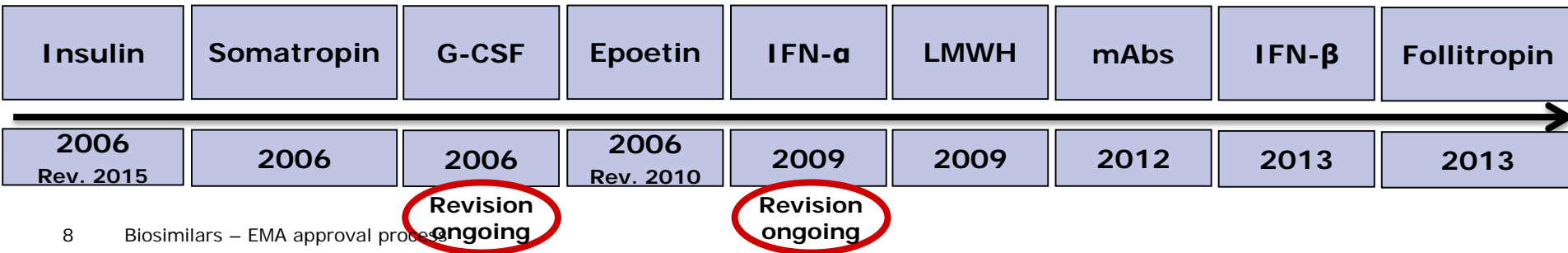
**Non-clinical/clinical  
Guideline**

Revised  
2015

**Quality Guideline**

Revised  
2014

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





# What is a biosimilar?

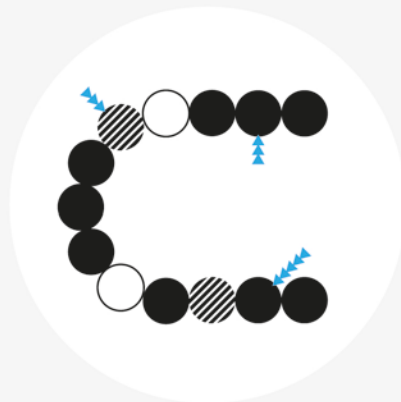
## Directive 2001/83/EC, Article 10(4):

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.

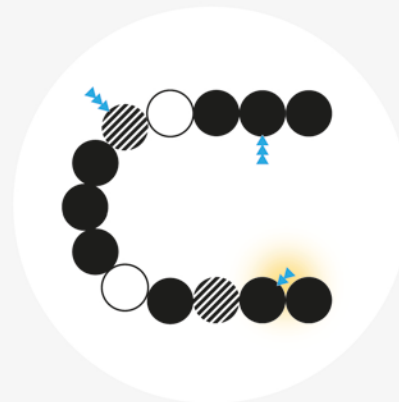
## “Overarching ” biosimilar guideline:

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?



**Reference medicine**



**Biosimilar medicine**

## 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

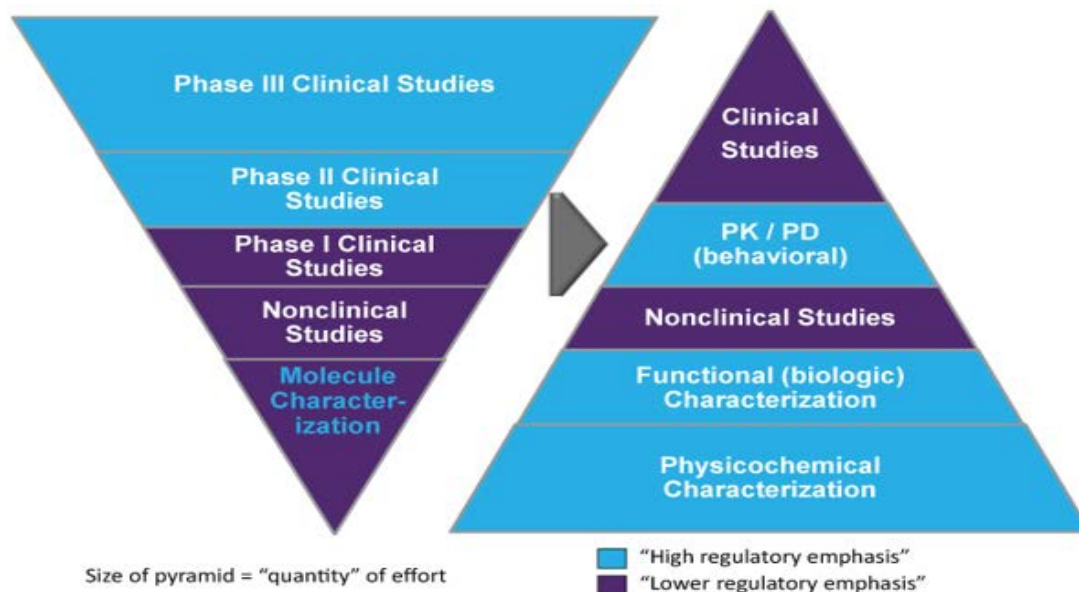
There should be no **clinically meaningful differences** between the two products

## 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<sup>3, 4, 5</sup>. 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 1<sup>st</sup> 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

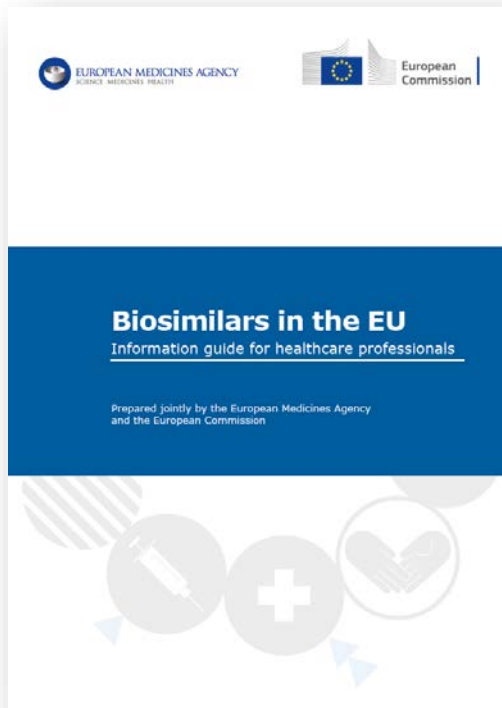
**However: Initial concerns of clinicians after Remsima authorisation (absence of IBD data)**

## 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 interchangeable 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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