MEDICAMENTOS BIOSIMILARES
Evidencias de Eficacia y Seguridad

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Disclosure

- Consultancy and academic fees from: Almirall, Amgen, Astellas, Astra-Zeneca, Bayer, Celltrion, Hospira, Lilly, Merck-Serono, Pfizer, Takeda.
- Member of the EMA-CHMP 2002-2011. Involvement in the development of the EMA policy on biosimilars and evaluation of the MAA of biosimilar medicinal products

Biosimilarity is an innovative regulatory and development concept

The aim is to create highly similar products with no clinically meaningful differences from their reference biologics in terms of safety, purity, and efficacy.

SAME
Active substance
Pharmaceutical form
Indications
Route of administration

EU definition

- A biosimilar is a biological medicinal product that contains a ***version of the active substance*** of an already authorized original biological medicinal product (reference medicinal product)
- A biosimilar demonstrates ***similarity*** to the reference medicinal product in ***terms of quality characteristics***, ***biological activity***, ***safety***, and ***efficacy*** based on a comprehensive comparability exercise

Weise M, et al. Nat Biotechnol. 2011;29:690-3.
Guideline on similar biological medicinal products. Available from: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf. Accessed September 2015.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15/02/2015

Medicine Name	Common name	Marketing Authorisation Holder	Authorisation date
Omnitrope	somatropin	Sandoz GmbH	12/04/2006
Abseamed	epoetin alfa	Medice Arzneimittel Pütter GmbH & Co. KG	28/08/2007
Binocrit	epoetin alfa	Sandoz GmbH	28/08/2007
Epoetin Alfa Hexal	epoetin alfa	Hexal AG	28/08/2007
Retacrit	epoetin zeta	Hospira UK Limited	18/12/2007
Silapo	epoetin zeta	Stada Arzneimittel AG	18/12/2007
Biograstim	filgrastim	AbZ-Pharma GmbH	15/09/2008
Ratiograstim	filgrastim	Ratiopharm GmbH	15/09/2008
Tevagrastim	filgrastim	Teva GmbH	15/09/2008
Filgrastim Hexal	filgrastim	Hexal AG	06/02/2009
Zarzio	filgrastim	Sandoz GmbH	06/02/2009
Nivestim	filgrastim	Hospira UK Ltd.	08/06/2010
Inflectra	infliximab	Hospira UK Limited	10/09/2013
Remsima	infliximab	Celltrion Healthcare Hungary Kft.	10/09/2013
Ovaleap	follitropin alfa	Teva Pharma B.V.	27/09/2013
Grastofil	filgrastim	Apotex Europe BV	18/10/2013
Bemfola	follitropin alfa	Finox Biotech AG	27/03/2014
Abasaglar	insulin glargine	Eli Lilly Regional Operations GmbH	09/09/2014
Accofil	filgrastim	Accord Healthcare Ltd	18/09/2014

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Por qué nos vuelve a preocupar algo que ya lleva usándose casi 10 años?

- Espectro terapéutico más amplio

  (mABs)

- Uso y dispensación no-hospitalarios

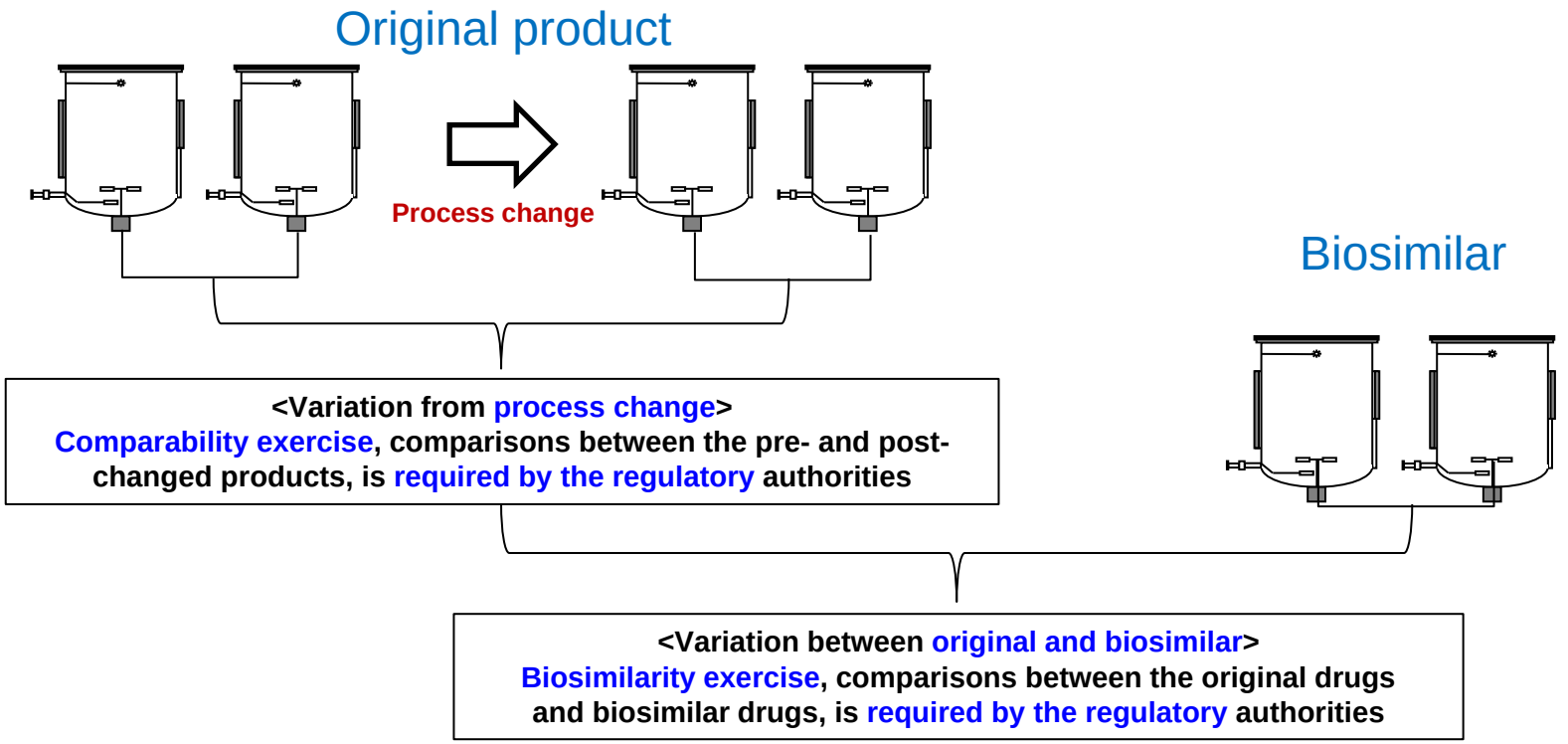
  (Insulina garglina)

- Biosimilares no recombinantes

  (LMWH)

The Similar-But-Not-Identical Paradigm

Biologics should not be identical between A and B batches due to its inherent variability, and process change is not unusual after approval.



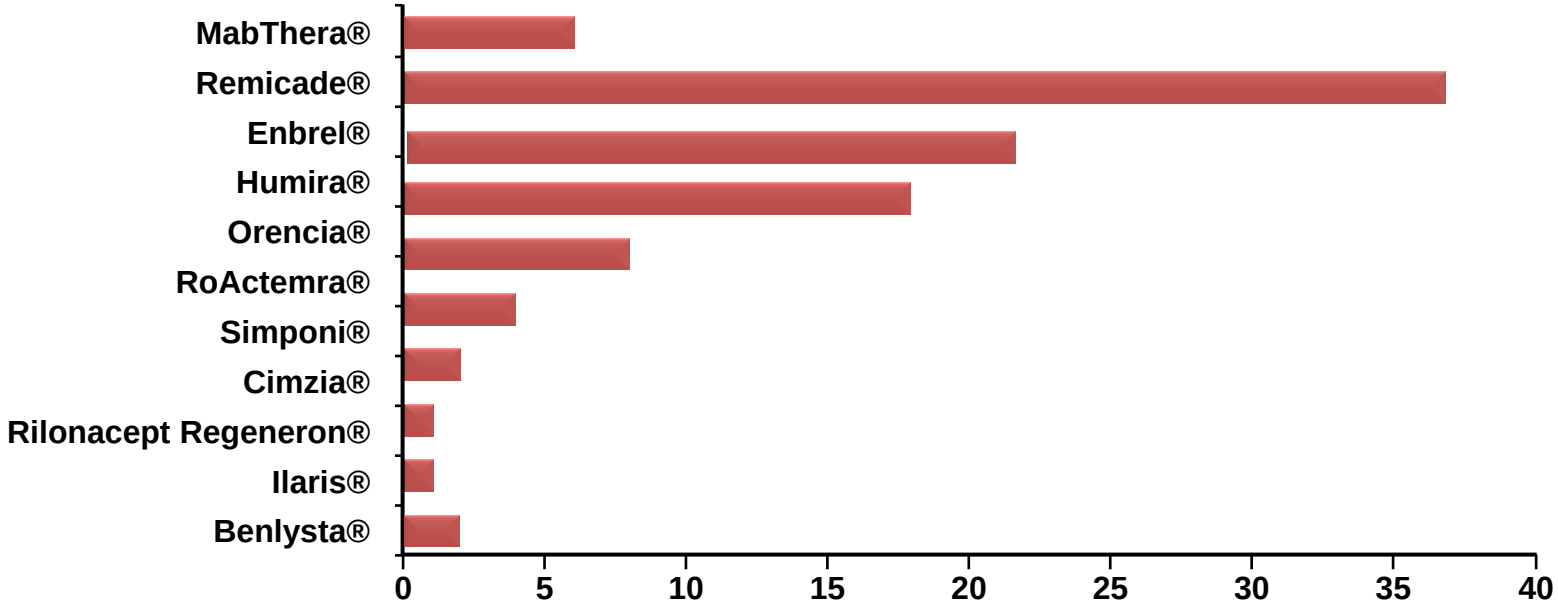
"From a scientific and regulatory point of view, the active substance of the biosimilar is just another version of the active substance of the originator product"

1. Biosimilars: the science of extrapolation, Blood, 2014

'Change in manufacturing process is common'

- Once biological products are approved, their product quality attributes may shift as the originator makes manufacturing process changes
- A comparability exercise is required for originator biological medicinal products when changes to the manufacturing process are made[1]

Changes in the manufacturing processes for biologics used in rheumatologic indications from time of first approval in Europe[2]



1. Weise et al. *Blood* 2014; 124: 3191-3196
2. Schneider *Ann Rheum Dis* 2013; 13: 315-318

No se espera de un BS que deba establecer el B/R en todas las indicaciones del innovador

How much information do we need?

Idea: C. Nick

www.lucky-lions.com

To reasonably rule-out clinically relevant dissimilarity

Biosimilar references in Europe

Define principles

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

General recommendations

- Quality
- Non clinical
- Clinical

Drug-specific recommendations

- Insulin
- rGH
- G-CSF
- Epoetin
- FSH
- IFN
- LMWH
- mAbs

RMP

GENERIC

BIOSIMILAR

Paso 1: Comparabilidad cualitativa

Characteristic Analyzed	Analytical Method
Primary structure	Peptide mapping
Higher order	Disulphide bond analysis
Content	Protein concentration
Purity (aggregates and fragments)	Analytical ultracentrifugation
Isoforms (charge variants)	Ion-exchange chromatography
Glycosylation	Oligosaccharide profile

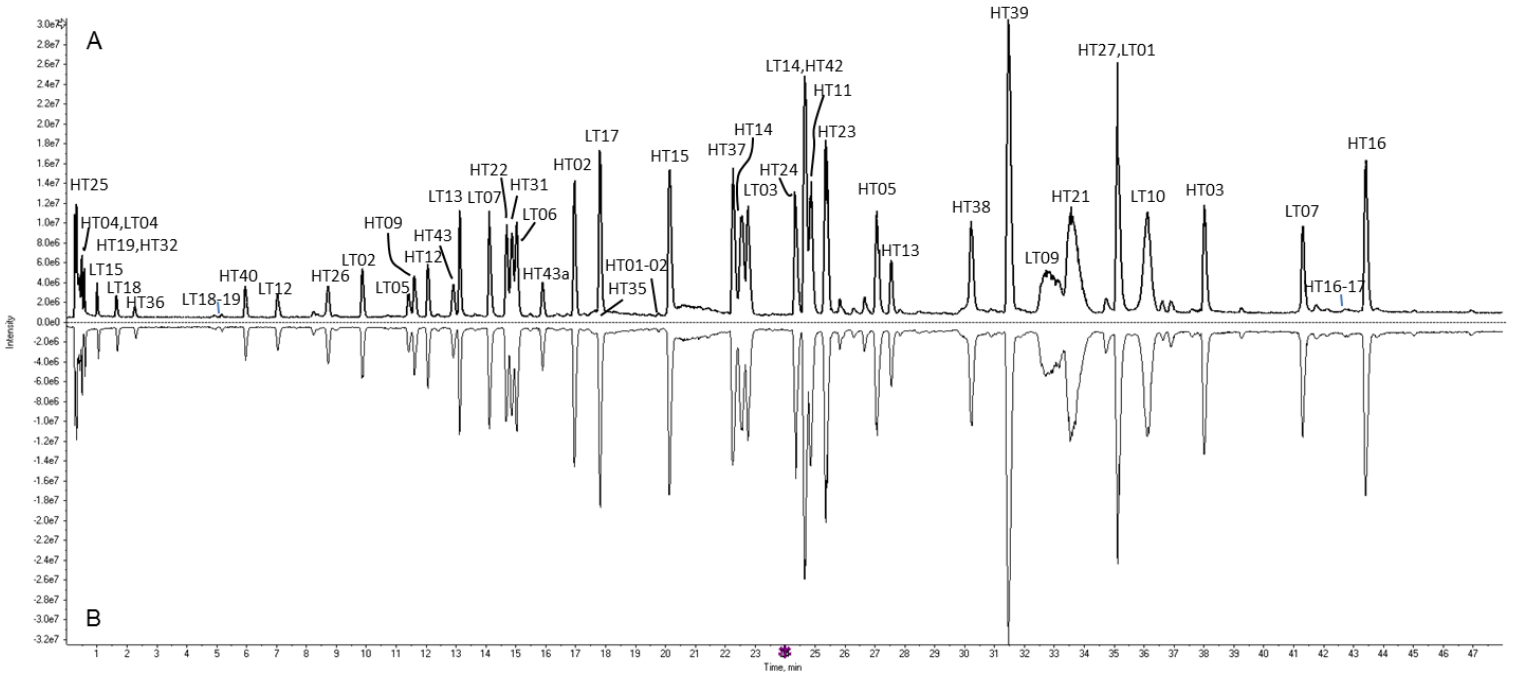
EMA Guideline on similar biological medicinal products containing Biotechnology-derived proteins as active substance: quality issues.
EMEA/CHMP/BWP/49348/2005

Physicochemical and biological studies for comparability of infliximab: Primary Structure

- **Peptide mapping / MS/MS analysis**
  Determine primary structure

Remsima

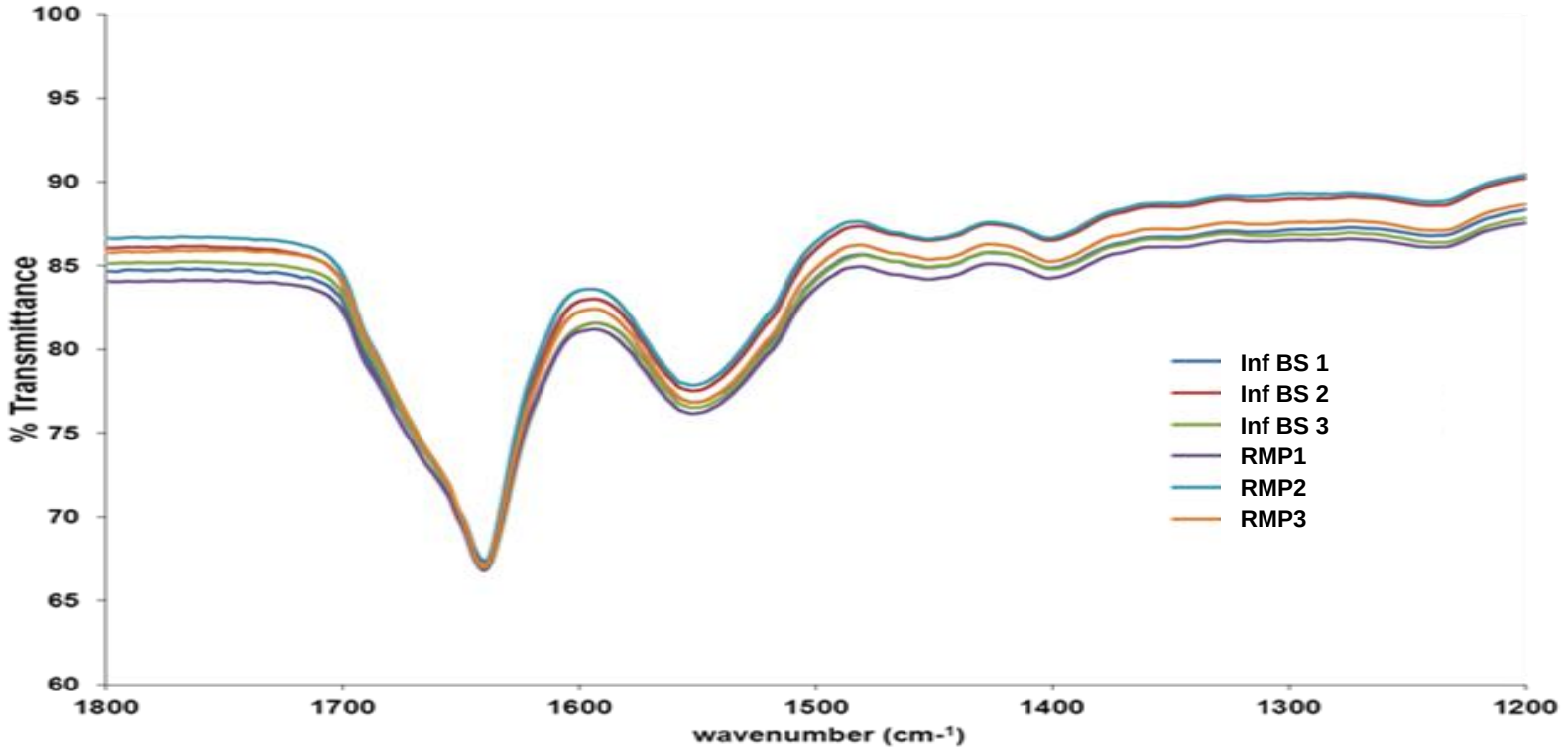
RMP

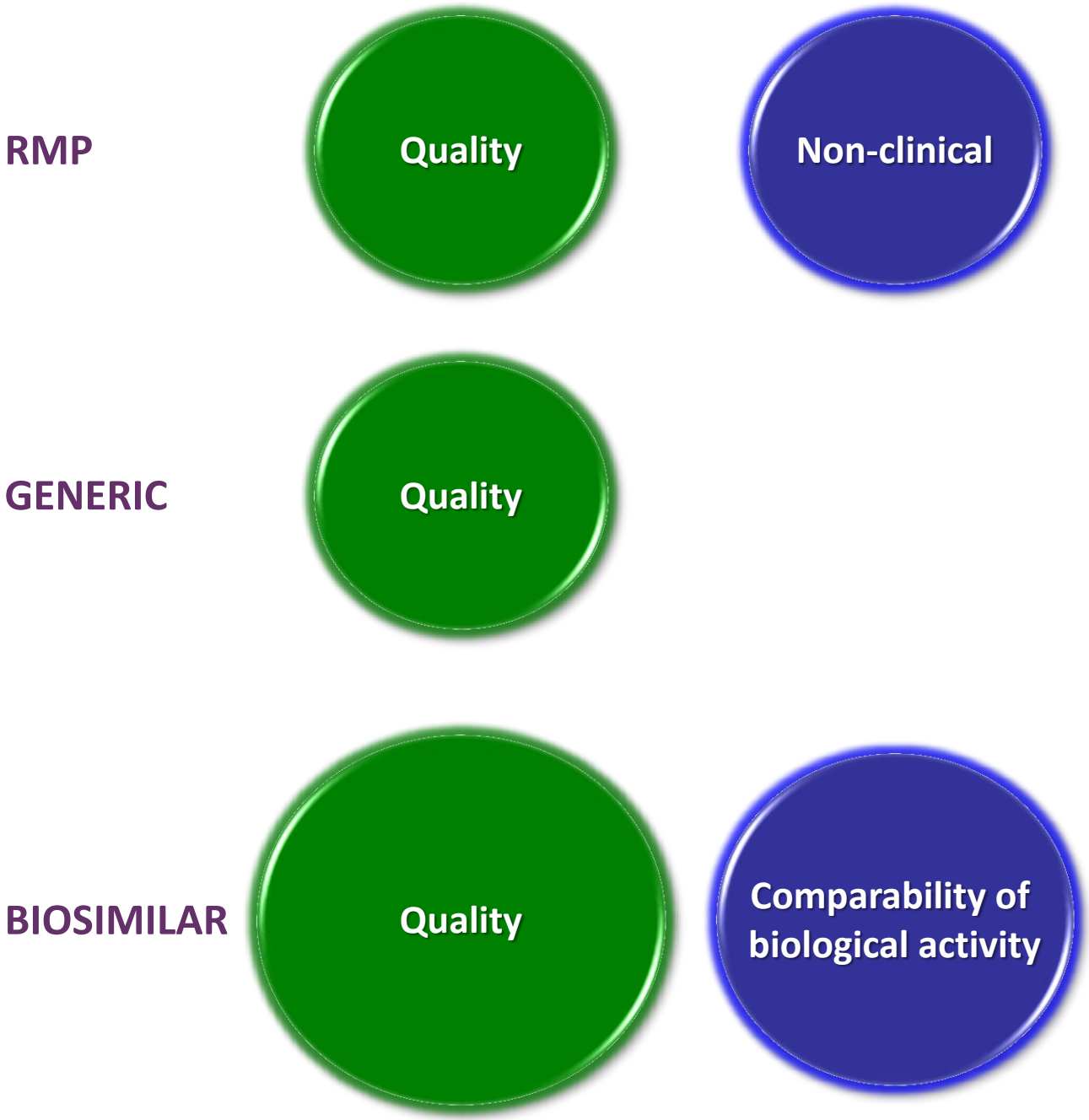


Equivalent: Sequence Coverage: 100 %

Physicochemical and biological studies for comparability of Remsima: Higher Order Structure

- **Fourier Transform Infrared Spectroscopy (FTIR)**
  Determine secondary in terms of amide bond and hydrogen bond




RMP
Quality
Non-clinical
GENERIC
Quality
BIOSIMILAR
Quality
Comparability of biological activity

Paso 2: Comparabilidad no clínica

- Al igual que con cualquier biológico, con el biosimilar se llevan a acabo **estudios preclínicos** previos a los ensayos clínicos en humanos.

- Los datos son generados a través de un programa de estudios realizados en modelos animales o humanos adecuados:

  - *Estudios In vitro*
    - Unión a la diana (ej: receptores , antígenos, enzimas)
    - Transducción de señal y actividad funcional / viabilidad de células relevantes.
    - Se toma la decisión si se requiere alguna evaluación in vivo

  - Si se considera necesaria una evaluación *in vivo*, el enfoque de los estudios será farmacocinético y/o farmacodinámico y/o de seguridad)
    - Depende de la necesidad de información adicional

EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. EMEA/CHMP/BMWP/42832/2005 Rev. 1. 03 June 2013

Biological activity of insulins

- Binding to IR-A and IR-B
  - Either cells artificially expressing IR-A and IR-B
  - Or cell lines with endogenous expression of IR-A or IR-B are employed, it has to be demonstrated that indeed only one receptor subtype is present.
- Comparative IGF-1 receptor binding
- Functional assays
  - glycogen formation
  - lipogenesis
  - inhibition of stimulated lipolysis
  - glucose transport

Biological activity of anti-TNF

F(ab')2-related	Fc-F(ab')2-related	Fc-related
In Vitro TNFα Neutralization	Suppression of T Cell Proliferation by Induced Regulatory Macrophages in MLR Assay	C1q Binding Affinity
TNFα Binding Affinity (ELISA)	Quantitation of Induced Regulatory Macrophages by FACS Analysis	Binding to Fc Receptors • FcγRIIIa (V Type) / FcγRIIIa (F Type), FcγRIIIb, • FcγRIIa, FcγRIIb • FcγRI • FcRn
Cell Based Binding Affinity	Induced Regulatory Macrophage-mediated Wound Healing	Ex Vivo Binding to NK Cells • 1% BSA • 50% Serum
Apoptosis (FACS) by Reverse Signaling	CDC	
Inhibition of Cytokine Release by Reverse Signaling	ADCC in NK, PBMCs & WB • NK Cells • PBMCs • Whole Blood	
Suppression of Cytokine Secretion in Caco-2 Cells by Blocking sTNFα	ADCC using LPS-stimulated Monocytes as Target Cells. Expression Level of tmTNFα on Monocyte/Macrophages from IBD Patients	

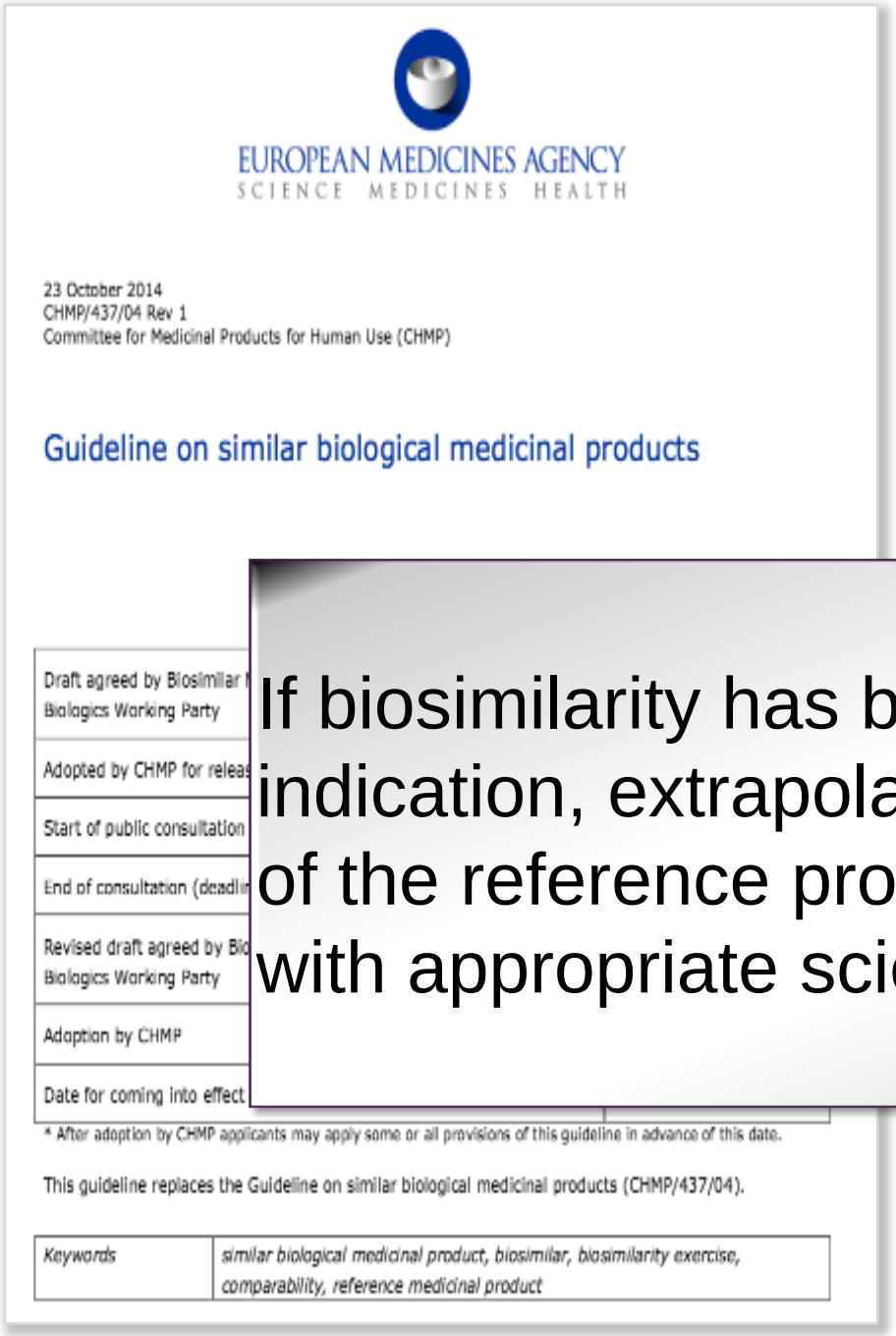

RMP
Quality
Non-clinical
Clinical
GENERIC
Quality
BE
BIOSIMILAR
Quality
Comparability of biological activity
Clinical

Paso 3 : Comparabilidad clínica

- Un biosimilar tiene que demostrar que es clínicamente equivalente al biológico de referencia en términos de eficacia y seguridad.

- La **información clínica necesaria** incluye:
  - Estudios comparativos farmacocinéticos (FC)
    - Se debe utilizar el modelo/población más sensible, ej: aquella con menos factores que puedan causar más variabilidad interindividual.
  - Si son factibles, estudios farmacodinámicos (FD).
  - Ensayos clínicos comparativos de eficacia y seguridad del biosimilar con el biológico de referencia.

EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. EMEA/CHMP/BMWP/42832/2005 Rev. 1. 03 June 2013



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Guideline on similar biological medicinal products

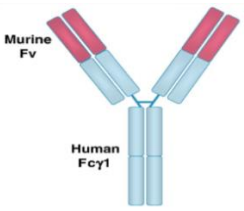
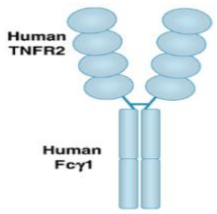
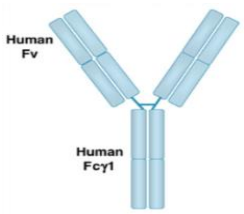
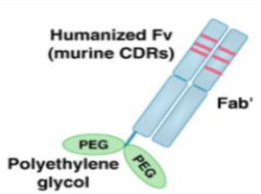
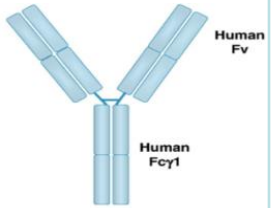
Draft agreed by Biosimilar … Biologics Working Party	
Adopted by CHMP for releas…	
Start of public consultation	
End of consultation (deadli…	
Revised draft agreed by Bio… Biologics Working Party	
Adoption by CHMP	
Date for coming into effect	

* After adoption by CHMP applicants may apply some or all provisions of this guideline in advance of this date.

This guideline replaces the Guideline on similar biological medicinal products (CHMP/437/04).

Keywords	*similar biological medicinal product, biosimilar, biosimilarity exercise, comparability, reference medicinal product*

If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification

	Infliximab	Etanercept	Adalimumab	Certolizumab	Golimumab
Brand name	REMICADE	ENBREL	HUMIRA	CIMZIA	SIMPONI
Structure					
US-licensed indications	RA, AS, PsA, Ps, CD, UC	RA, AS, JIA, PsA, Ps	RA, AS, JIA, PsA, Ps, CD, UC	RA, AS, PsA, CD	RA, PsA, AS, UC
EU-approved indications	RA, AS, PsA, Ps, CD, UC	RA, AS, JIA, PsA, Ps	RA, AS, JIA, PsA, Ps, CD, UC	RA, AS, PsA	RA, PsA, AS, UC

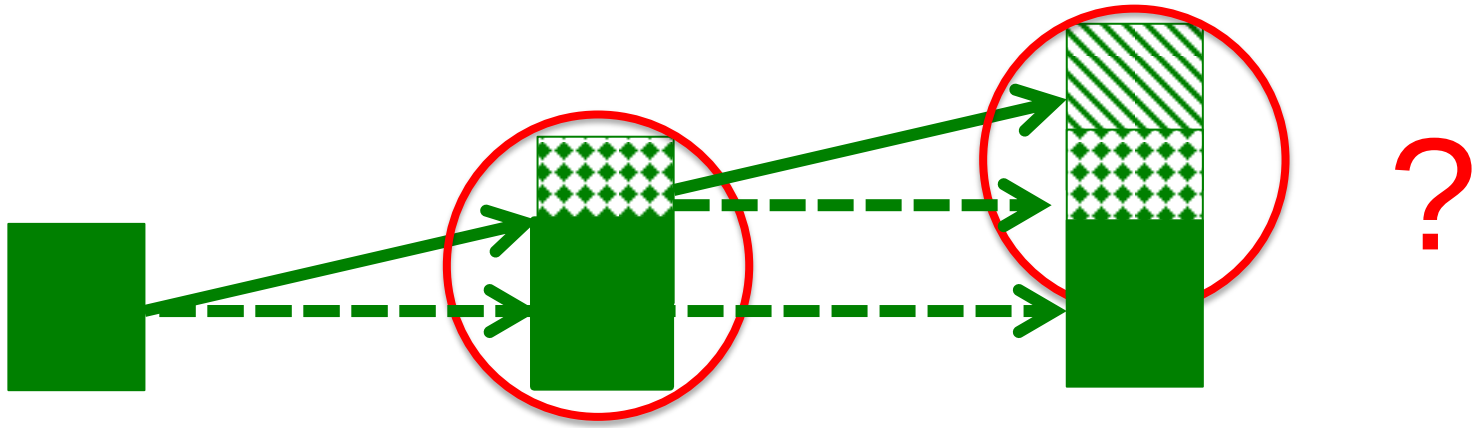
- RA, rheumatoid arthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; Ps, psoriasis; CD, Crohn’s disease; UC, ulcerative colitis; JIA, juvenile idiopathic arthritis

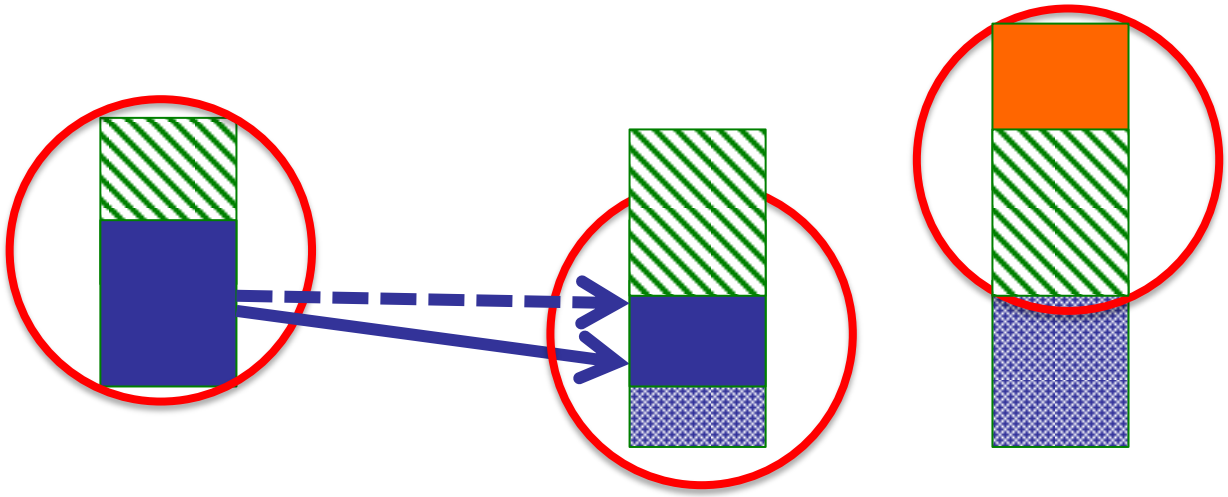
3. General principles

3.1. Application of the biosimilar approach

- 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.


UP
DOWN
PBS





Algunas consideraciones

El cambio es posible (siempre deseable?)

- ✓ ¿Puede garantizarse siempre un cambio seguro?
- ✓ Si el paciente está bien controlado con un medicamento (INNOVADOR o BIOSIMILAR), ¿qué razón para cambiarlo más allá de la puramente económica?
- ✓ ¿Justifica cualquier ahorro monetario cualquier riesgo?

Niveles de decisión

- ✓ Política hospitalaria – Gerencia/Dirección
- ✓ Decisiones colegiadas –CFTs o Comisiones interdisciplinarias
- ✓ Decisiones individuales paciente/prescriptor

Pensando en voz alta…

Las toma de decisiones individuales no debe dejar al margen a quienes han de asumir las consecuencias de tales decisiones

En el caso de las decisiones terapéuticas:
El paciente y su médico

No sería sensato asumir las consecuencias de decisiones que otros toman por nosotros

Qué opciones existen?

CONFRONTACIÓN-IMPOSICIÓN vs. COLABORACIÓN

Legalidad?

Bases científicas sólidas para garantizar un cambio seguro?

Inteligencia emocional?

Es una buena opción para los biosimilares?

Merece la pena teniendo en cuenta el margen de eficiencia conseguido?

SOCIEDAD ESPAÑOLA
FARMACIA HOSPITALARIA

SOCIEDAD ESPAÑOLA DE Farmacología clínica

POSICIONAMIENTO SOBRE IDENTIFICACIÓN, INTERCAMBIABILIDAD Y SUSTITUCIÓN DE MEDICAMENTOS BIOSIMILARES

http://www.se-fc.org/gestor/images/documentos/intercambiabilidad%20biosimilares.pdf

L**a introducción de biosimilares en el Sistema Nacional de Salud (SNS)** es positiva

Un medicamento biosimilar autorizado en la UE es **“prescribible”** con garantías de eficacia y seguridad en todas las indicaciones autorizadas en su ficha técnica

Los medicamentos biológicos, incluidos los biosimilares, deben **prescribirse por marca comercial**

Debe garantizarse un circuito de prescripción, dispensación, administración y registro utilizando la marca comercial.

Responsabilidad del médico en la sostenibilidad del SNS

La **sustitución** de una marca por otra en el momento de la dispensación a un paciente está **prohibida**. Ni el ámbito hospitalario ni el amparo de comisiones colegiadas en las que haya médicos (por ejemplo la Comisión de Farmacia) pueden suplantar la responsabilidad del médico prescriptor ante un paciente.

La **no sustitución** y la recomendación de no cambiar de marca a un paciente, en ausencia de motivos médicos para ello, se justifica por varias razones:

- la ausencia de demostración de intercambiabilidad
- la necesidad de atribuir las reacciones adversas que ocurran a cada marca concreta
- la repercusión que el cambio puede tener en la adherencia del paciente o en el entrenamiento en el uso de un dispositivo concreto.
- la posible generación de dudas y desconfianza en médicos y pacientes

Los concursos y acuerdos para la adquisición de biosimilares deben respetar los principios mencionados

GRACIAS