MINISTERIO
DE SANIDAD, CONSUMO
Y BIENESTAR SOCIAL

agencia española de
medicamentos y
productos sanitarios

Biosimilares
Eficacia, Seguridad, Calidad

Antonio Blázquez Pérez. AEMPS.

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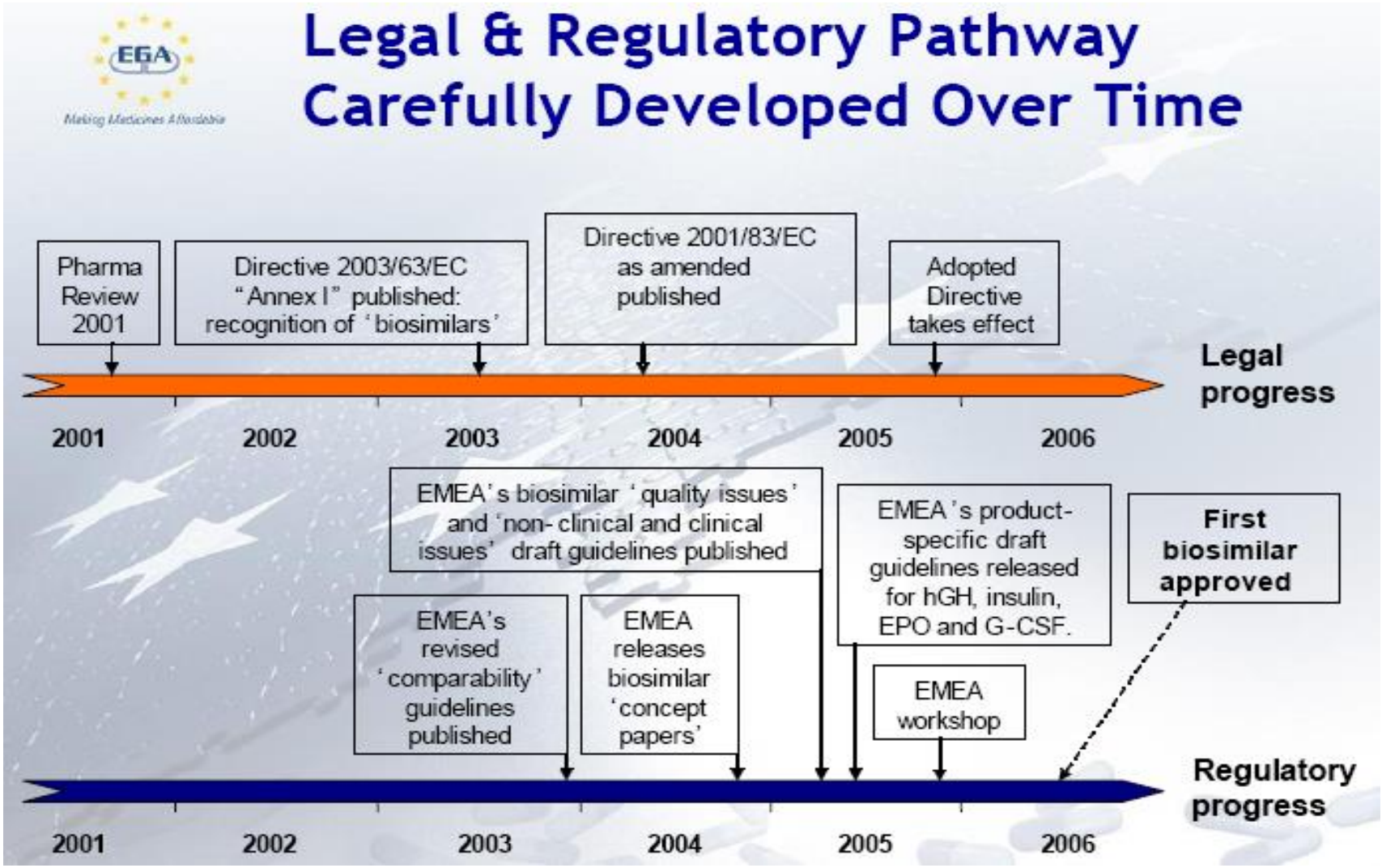
Biosimilares

- *¿Qué son?*
- *Demostración de eficacia/seguridad*
- *Extrapolación de Indicaciones*
- *Farmacovigilancia*
- *Sustitución*

EU+ Noruega, Islandia y Liechtenstein

http://www.ema.europa.eu/



Definición – *"no es un genérico….pero"*

Directiva 2001/83/EC (consolidada a 2009)

Artículo 10(1) **Genérico**

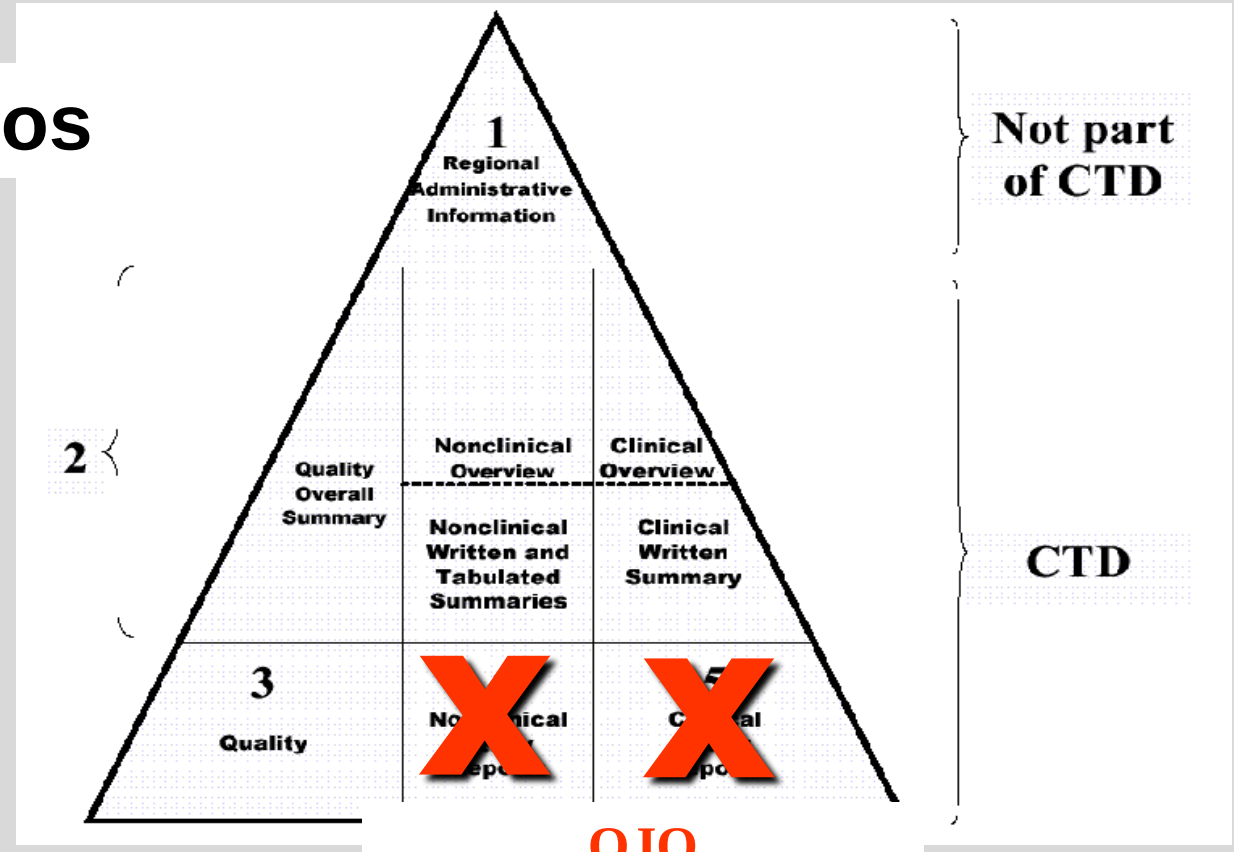
Artículo 10(3) **Híbrido**

Artículo 10(4)

Cuando un medicamento biológico que sea similar a un producto biológico de referencia no cumpla las condiciones de la definición de medicamentos genéricos, debido en particular a diferencias relacionadas con las materias primas o diferencias en el proceso de fabricación del medicamento biológico y del medicamento biológico de referencia, deberán aportarse los resultados de los ensayos preclínicos o clínicos adecuados relativos a dichas condiciones. El tipo y la cantidad de datos suplementarios deben ajustarse a los criterios pertinentes expuestos en el anexo I y a las directrices detalladas afines. No será necesario aportar los resultados de otras pruebas a partir del expediente del medicamento de referencia.

Contenido del expediente de registro según su base legal

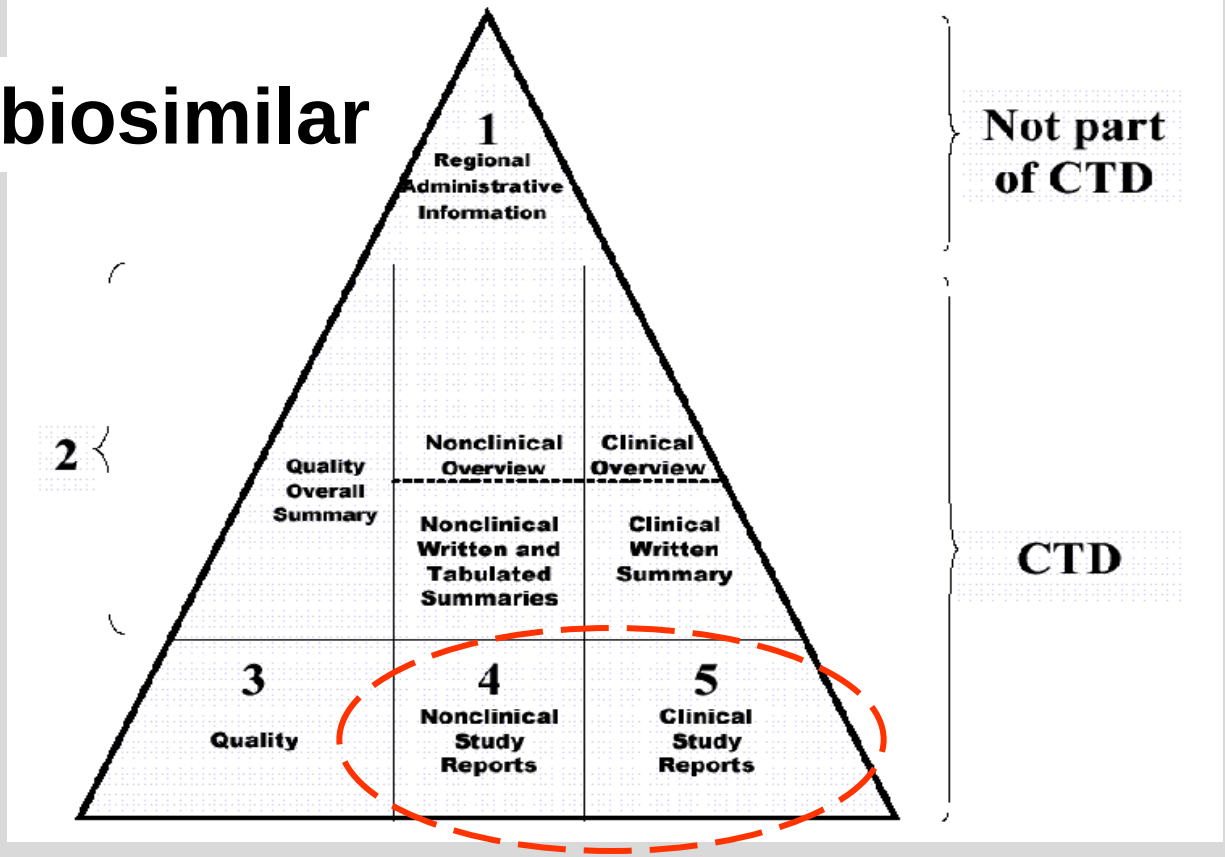
Genéricos



OJO
BIOEQUIVALENCIA

Contenido del expediente de registro según su base legal

Híbrido y biosimilar



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Definición – *"producto biológico"*

¿Que es un producto biológico?

- Asunciones :
- De origen biológico
- No es posible una caracterización completa
- Altamente dependiente del proceso de fabricación

Productos Biológicos en EMA

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TAMAÑO y COMPLEJIDAD

Inmunogenicidad

Mecanismo de acción no completamente establecido

Actualmente problemas técnicos para demostrar igualdad en el principio activo

¿Qué nos depara el futuro?

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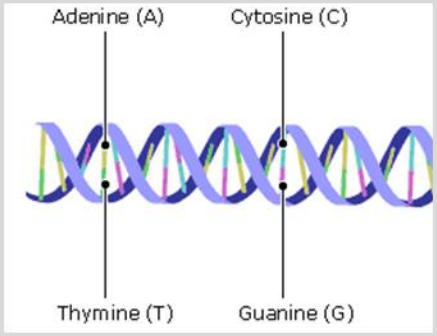
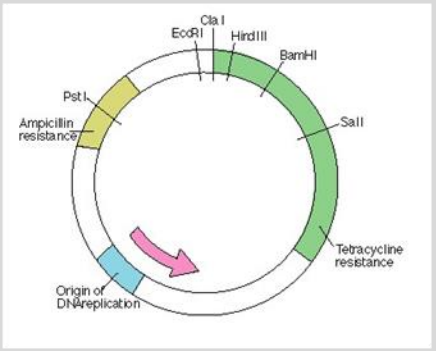
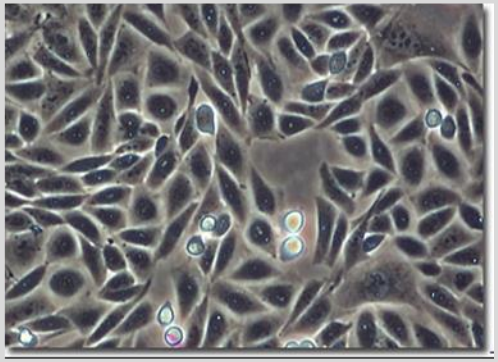
Problemas inherentes al método de fabricación para conseguir el mismo producto



Secuencia de ADN



Clonado

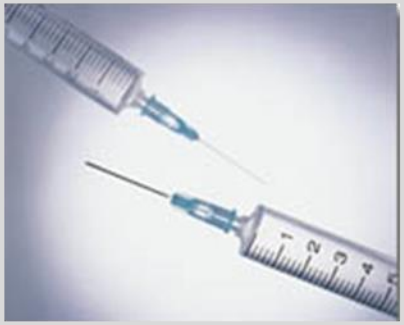


Expresión celular

UN PROCESO, UN PRODUCTO

Fermentación

Purificación



Formulación

Procedimiento centralizado

- Los biosimilares **GENERALMENTE** son autorizados con este procedimiento porque son "productos biotecnológicos"

1.1 Medicinal products derived from biotechnology

Persons wishing to obtain a marketing authorisation for a medicinal product developed by means of one of the following biotechnological processes:

- Recombinant DNA technology,
- Controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
- Hybridoma and monoclonal antibody methods

must submit the application to the EMEA and the application will be processed via the centralised procedure, as such products fall within the scope of Article 3(1) and point 1 of the Annex to the Regulation.

NOTICE TO APPLICANTS / VOLUME 2A / Procedures for marketing authorisation / CHAPTER 4 / Centralised Procedure / April 2006

Procedimiento centralizado

Rapporteur

Co-Rapporteur

Single Joint AR
(Rapp+Co-Rapp)

CHMP

Comisión Europea

Procedimiento centralizado

- Es el mismo comité, mismos expertos y evaluadores que **autorizan toda la innovación en materia de medicamentos** en Europa.

- Es el mismo comité, mismos expertos y evaluadores que autorizan la mayoría de las **variaciones de los medicamentos innovadores** en Europa.

Hormona Crecimiento

1.Omnitrope

2.Valtropin

Epoetina

3. Binocrit, Epoetin-alpha Hexal, Abseamed)

4. Silapo, Retacrit

Epostim, retirado

IFN-alfa

Alpheon, rechazado

Folitropin Alfa

9. Ovaleap

11. Bemfola

G-CSF

5.Biograstim
Ratiograstim
Filgrastim
Ratiopharm
Tevagrastim

6.Filgrastim Hexal Zarzio

7.Nivestim

10.Grastofil

13.Accofil

32.Pelgraz

Infliximab

8.Inflectra, Remsima

15. Flixabi

30. Zessly

Enoxaparina

16.Inhixa

Insulinas

Insulinas Marvel retirado

Solumarv rechazado

12.Insulina Glargina (Abasria)

18.Insulina Glargina (Lusduna)

22.Insulina Lispro (Sanofi)

28.Semglee

Etanercept

14. Benepali

21. Erelzi

Bevacizumab

26.Mvasi

Teriparatide

17.Terrosa, Movymia

Rituximab

18.Truxima

20.Ryximio, etc

Adalimumab

19.Solymbic, Amgevita

23.Imraldi

24.Cyltezo

31.Hirymoz, Halimatoz, Hefiya

Trastuzumab

25.Ontruzant

27. Herzuma

29. Kanjinti

32. Trazimera

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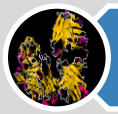
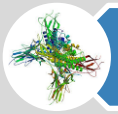
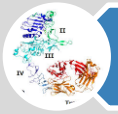
Próximos Biosimilares

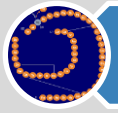

Infliximab*,**

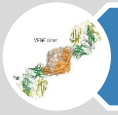

Adalimumab*


Filgrastim Pegilado*,**


Trastuzumab *,**


Bevacizumab*


Insulina **


Ranibizumab

Rituximab*

Etanercept*

*en evaluación **pendiente autorización Comisión

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¿Cómo demuestran esa similitud que les confiere seguridad/eficacia?

Caracterización

Producto de síntesis química.

…Descripción del producto

Identificación por IR, HPLC

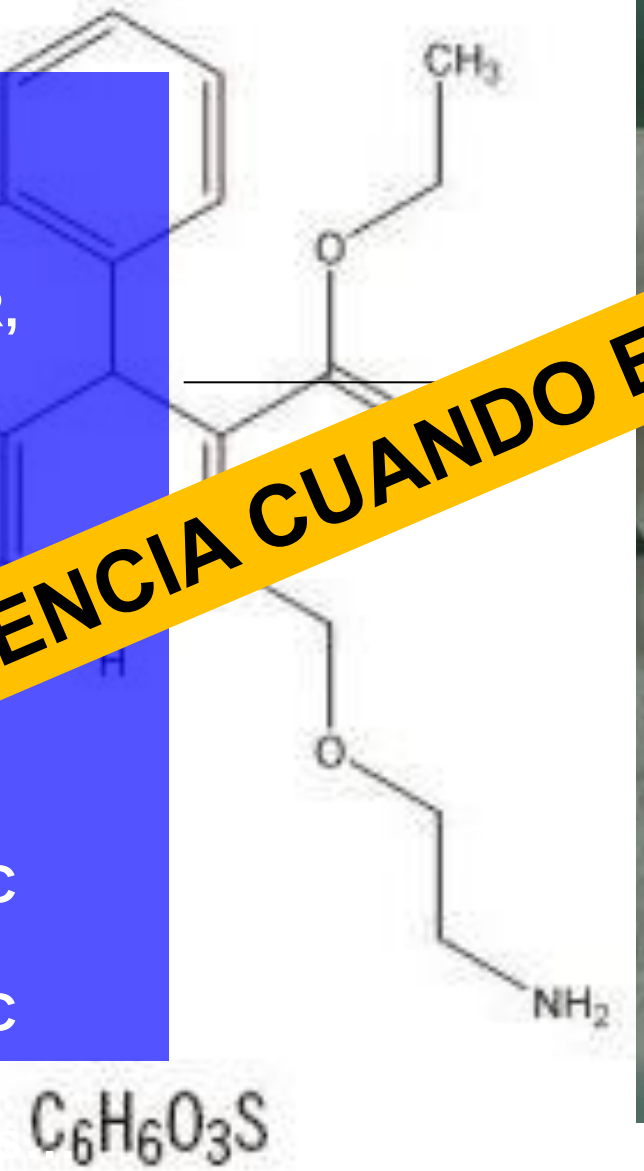
Contenido en agua

Metales pesad…

Ce… …tadas

I…purezas por HPLC

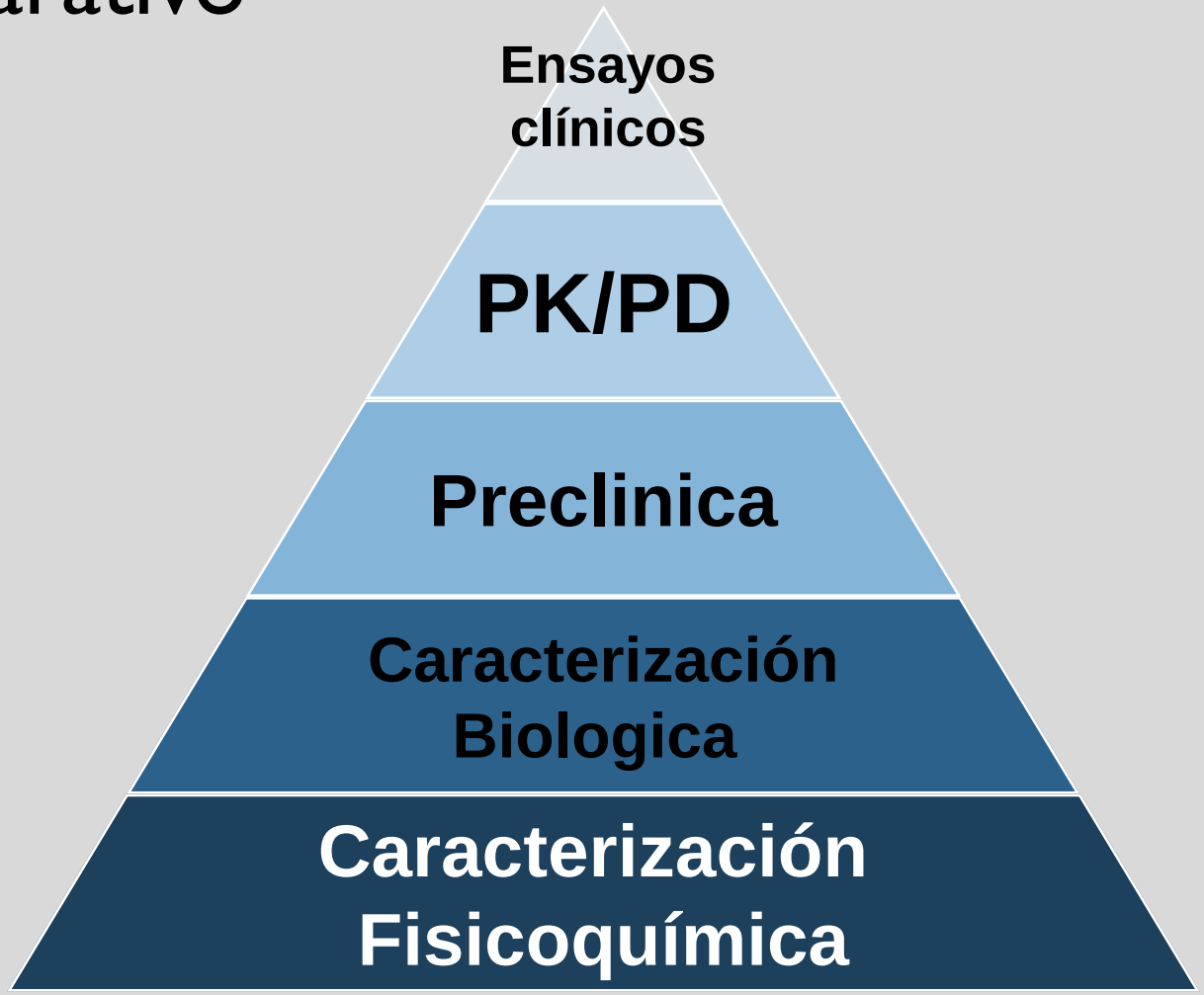
Contenido por HPLC



BIOEQUIVALENCIA CUANDO ES NECESARIA

Biosimilares

Ejercicio comparativo



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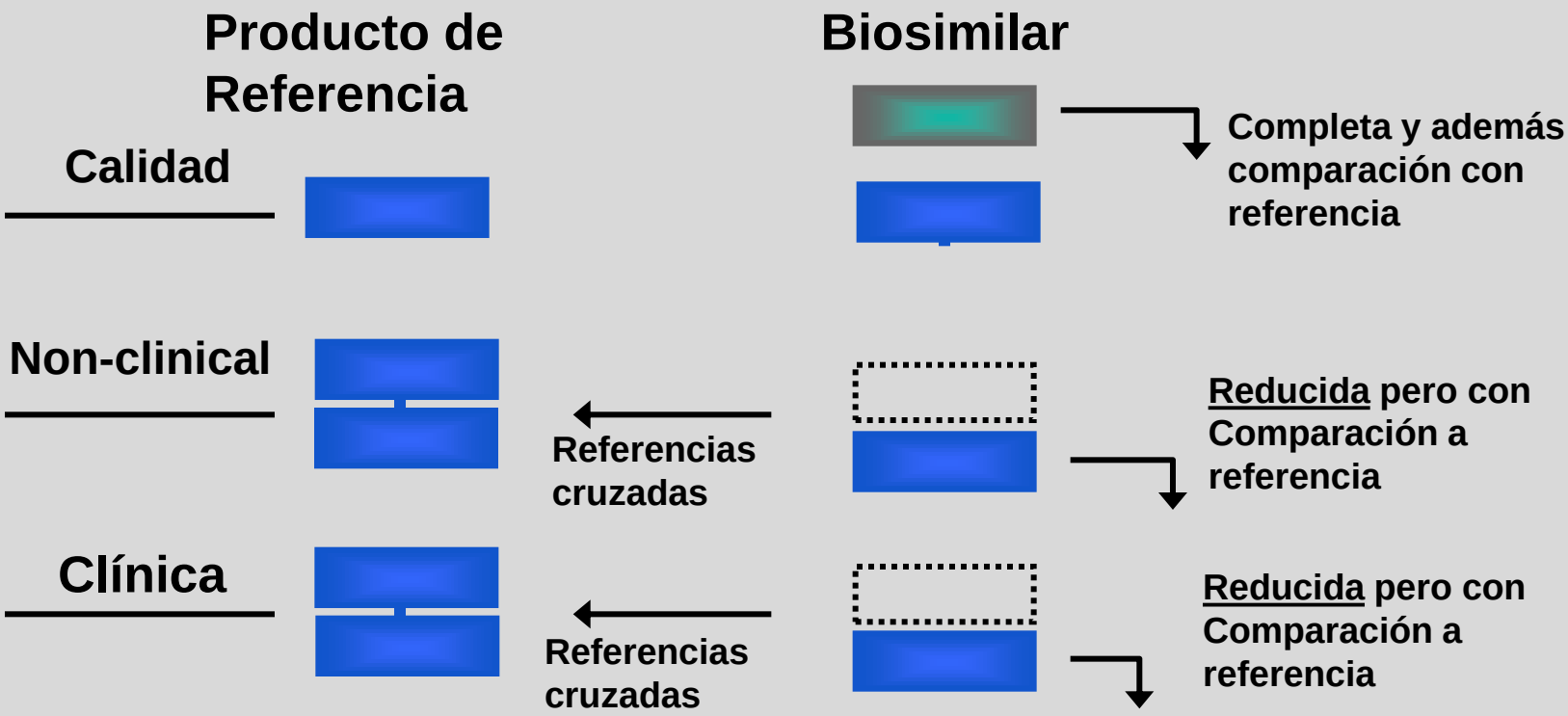
Biosimilares

Ejercicio comparativo

Enfoque clínico

Requisitos en biosimilares

Stepwise comparison & head-to-head comparison



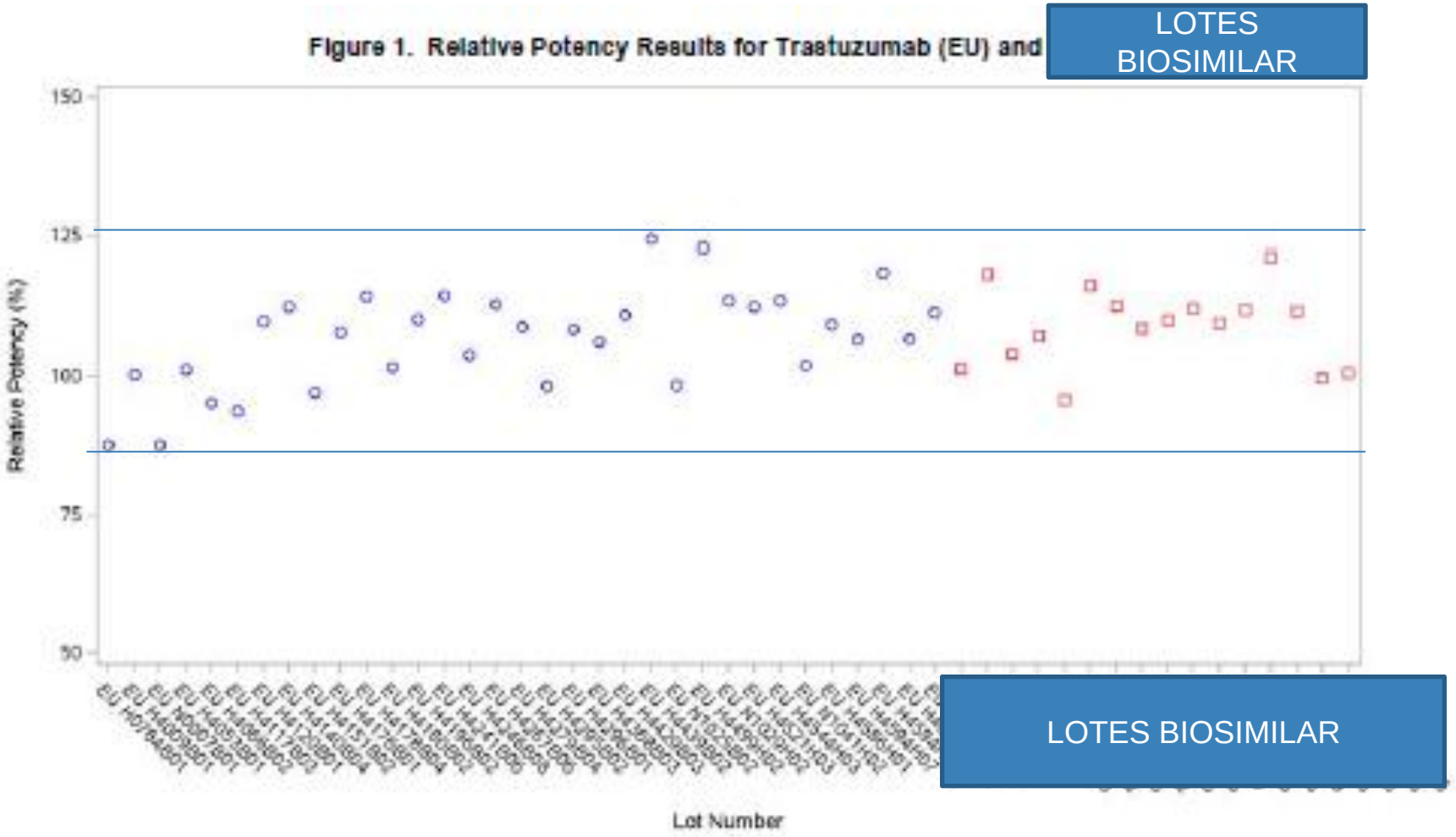
Source: Modified from EMA P. Richardson and P. Celis (2007), *1st Drug Evaluation Forum*, Pharm. Soc. Japan

Caracterización

Molecular Parameter	Attribute	Methods for control and characterisation
Primary structure	Amino acid sequence	Orthogonal peptide maps with high-resolution MS and MS/MS sequencing; N-terminal sequencing
	Disulfide bridging	Non-reducing peptide mapping
	Free cysteines	Ellman's assay, non-reducing peptide mapping
	Thioether bridging	Peptide mapping, -, CE-
Higher order structure	Secondary and tertiary structure	CD spectroscopy
Molecular Mass/Size	Molecular mass	MALDI-ToF; -MALLS;
	Molecular size	SEC, -PAGE (reducing/non-reducing with colloidal Coomassie and/or silver staining); CE-; DLS
Charge	Degree of sialylation	AEX
	Charge/Size	2D-
Heterogeneity: Glycosylation	N-glycan isoforms: Major (bG0, bG1, bG2) Minor (e.g. unfucosylated, α-Gal)	NP-HPLC (after sialidase digestion) of 2AB labelled glycans coupled to -MS, exoglycosidase digestion followed by NP-HPLC
	O-Glycans	MALDI-ToF of released O-glycans (after sialidase digestion)
	Glycosylation site occupancy and site specific (e.g. Fc part)	Peptide mapping coupled to -MS
	N-glycan analysis	
	Sialic Acids incl. NGNA (N-glycolylneuraminic acid)	Overall sialylation by AEX, WAX of 2-AB labelled N-glycans, NP-HPLC of 2AB labelled N-glcycans coupled to -MS, exoglycosidase digestion, MALDI-ToF of chemically released O-glycans ,RP-HPLC of DMB labelled sialic acids released from N- and O-glycans
Heterogeneity: AA-sequence	Variability of N-terminus (− Leu, − Leu-Pro)	Peptide Mapping
	Variability of C-terminus: − , truncation to proline amide	Cation exchange chromatography of the desialylated molecule; Peptide Mapping
Heterogeneity: Size	Aggregation	, FFF, SEC/FFF-MALLS, DLS, AUC
	Fragmentation	, CE-, -PAGE
Amino acid modifications	Oxidation	RP-HPLC, Peptide Mapping
	Deamidation	CEX; Peptide Mapping, IEF of desialylated molecule

	Test	Method / cell line	Used for
Binding assays	TNF-αγ binding assay	Surface plasmon resonance assay	Characterisation, comparability
	FcγRIII binding assay	Surface plasmon resonance assay	Characterisation, comparability
	FcγRn binding assay	Surface plasmon resonance assay	Characterisation, comparability
In-vitro bioassays	TNF-αγneutralisation reporter gene assay	Recombinant HEK293 cells expressing NFkB-luciferase reporter gene	Release of DS, early development phase, characterisation, comparability
	TNF-β neutralisation reporter gene assay	Recombinant HEK293 cells expressing NFkB-luciferase reporter gene	Early development phase, characterisation, comparability

The potency assay assesses ligand independent inhibition of HER2 signaling using a breast cancer cell line (BT-474) with constitutively high levels of HER2 expression.



HERZUMA

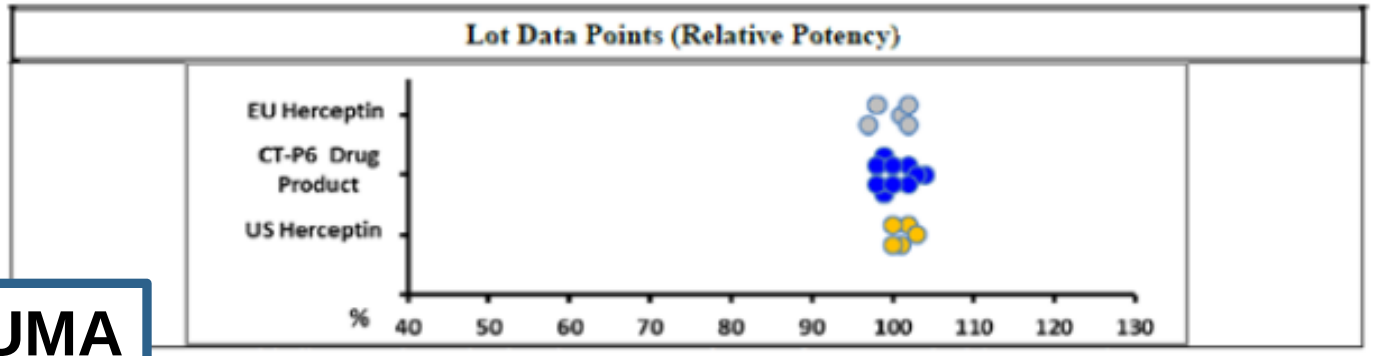


Figure 1: Scatter Plot for Inhibition of HER2 Extracellular Domain Cleavage Results

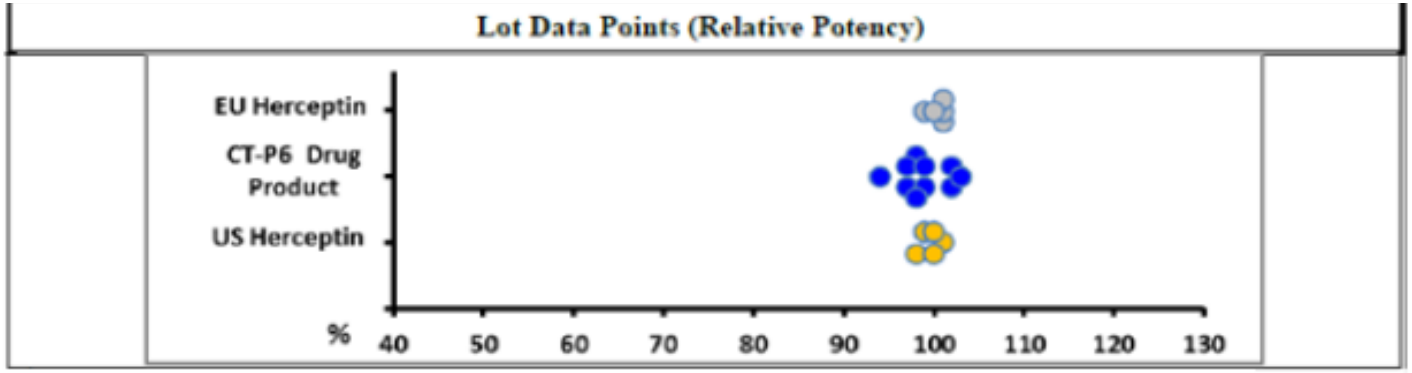


Figure 2: Scatter Plot for Down-Regulation of HER2 Expression Results

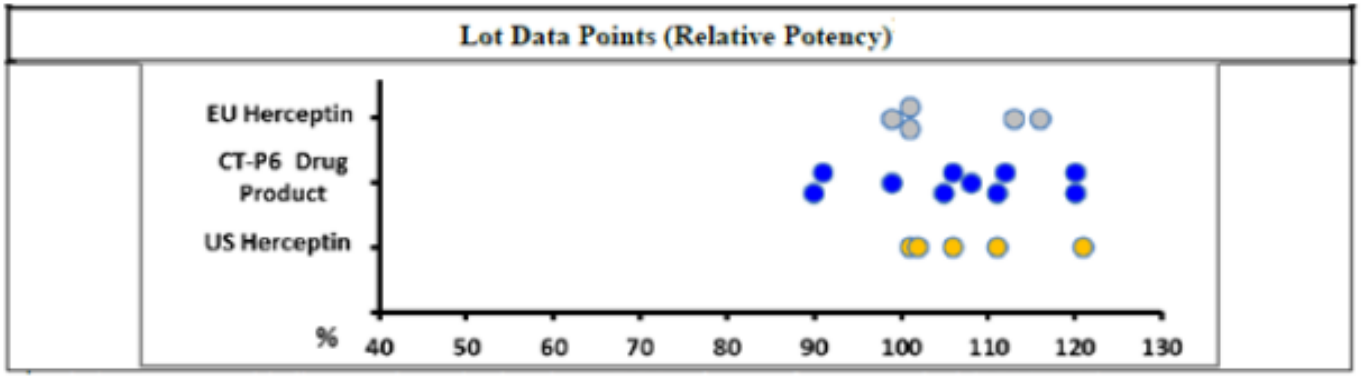


Figure 3: Scatter Plot for Induction of Cell Cycle Arrest Results

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Biosimilares en EMA:

Datos de Ensayos clínicos necesarios para aprobación

	Dose-Loading Phase			Maintenance Phase[1]	
	Dose 1 Week 0 (Day 0)	Dose 2 Week 2 (Day 14)	Dose 3 Week 6 (Day 42)	Dose 4, 5, & 6 Weeks 14, 22, & 30 (Days 98, 154, & 210)	Doses 7, 8, & 9 Weeks 38, 46, & 54 (Days 266, 322, & 378)
CT-P13[2]	X	X	X	X	X
Remicade[2]	X	X	X	X	X
Primary Efficacy Evaluation	←	—	—	→	
Week 30 Pharmacokinetic Evaluation	←	—	—	→	
Week 30 Pharmacodynamic Evaluation	←	—	—	→	
Week 30 Safety Evaluation	←	—	—	→	
Efficacy Evaluation	←	—	—	—	→
Pharmacokinetic Evaluation	←	—	—	—	→
Pharmacodynamic Evaluation	←	—	—	—	→
Safety Evaluation	←	—	—	—	→

1. Following Dose 3, further doses could be administered every 8 weeks up to Week 54 continuing with assigned treatment.
2. A dose visit window of ±3 days is allowed up to and including Dose 6; a dose visit window of ±5 days is allowed thereafter, including the End-of-Study Visit.

Table 28 Proportion of ACR20 responders at Week 30 (exact binomial method)

Treatment Group	n/N′ (%)	Estimate of Treatment Difference[1]	95% CI of Treatment Difference[2]
All-Randomized Population			
CT-P13	184/302 (60.9)	0.02	(–0.06, 0.10)
Remicade	178/304 (58.6)		
Per-Protocol Population			
CT-P13	182/248 (73.4)	0.04	(–0.04, 0.12)
Remicade	175/251 (69.7)		

ACR20, American College of Rheumatology definition of a 20% improvement; CI, confidence interval.
Note: N′=the number of patients with an assessment, n=the number of patients with the event, (%)=n/N′×100.

1. Estimate of the difference in proportions between the 2 treatment groups (CT-P13 – Remicade) using the exact binomial test.
2. Therapeutic equivalence was concluded if the 95% CI for the difference in proportions between the 2 treatment groups was entirely contained within the range -15% to 15%.

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Biosimilares en EMA:

Datos de Ensayos clínicos necesarios para aprobación

Primary endpoint

The primary endpoint was pathological complete response rate of the primary breast tumour. pCR was defined as no histological evidence of residual invasive tumour cells in the breast specimen removed at surgery [bpCR]. Non-invasive breast residuals were allowed and the pathological examination of axillary lymph nodes was not to be considered; ypT0/is, ypN0/+.

ONTRUZANT

Table 26: *Analysis of difference in tpCR rate*, **SB3-G31-BC**

Analysis Set	Treatment	n/n'	(%)	Adjusted Difference	95% CI
PPS	SB3 (N=402)	175/382	(45.8)	11.05%	[4.44%, 17.66%]
	EU Herceptin® (N=398)	136/380	(35.8)		
FAS	SB3 (N=437)	180/398	(45.2)	10.23%	[3.73%, 16.73%]
	EU Herceptin® (N=438)	142/397	(35.8)		

CI = confidence interval; FAS = Full Analysis Set; N = number of patients in Analysis Set; n = number of responders; n' = number of patients with available assessment results of pathological T category and N category in pN0 and pN+; PPS = Per-protocol Set; tpCR = total pathological complete response.
Percentages were based on n'.
The adjusted difference and its 95% CI were analysed by a stratified Cochran-Mantel-Haenszel test with hormone receptor status, breast cancer type, and region as factors.
For the FAS, only available data were included in the analysis.

KANJINTI

Table 6. Sensitivity Analyses: Risk Difference of Pathologic Complete Response in Breast Tissue and Axillary Lymph Nodes

Analysis	pCR[a] ABP 980 n/N (%)	Trastuzumab n/N (%)	RD (%)	95% CI	90% CI
Assessed by local laboratory					
PP population[b]	166/351 (47.3)	134/328 (40.9)	6.4	(-1.0, 13.8)	(0.2, 12.6)
ITT population using NRI[b]	172/364 (47.3)	137/352 (38.9)	8.1	(0.9, 15.3)	(2.0, 14.1)
ITT population using NRI: adjusted for correct	172/364 (47.3)	137/352 (38.9)	8.2	(1.0, 15.4)	(2.2, 14.2)
pCR evaluable population: adjusted for correct stratification factors[c]	172/358 (48.0)	137/338 (40.5)	7.4	(0.1, 14.7)	(1.3, 13.6)
pCR evaluable population: additional model covariates[d]	172/358 (48.0)	137/338 (40.5)	7.3	(0.0, 14.6)	(1.1, 13.4)
Assessed by central laboratory					
pCR evaluable population[b]	162/339 (47.8)	138/330 (41.8)	5.8	(-1.7, 13.2)	(-0.5, 12.0)
PP population[b]	156/333 (46.8)	137/321 (42.7)	4.1	(-3.5, 11.6)	(-2.3, 10.4)
ITT population using NRI[b]	162/364 (44.5)	138/352 (39.2)	5.1	(-2.0, 12.3)	(-0.9, 11.1)

Table 2. Summary of Pathologic Complete Response, Adjusting for Subjects Exposed to Trastuzumab with ADCC Activity Levels ≤ 65%, Quantified Using PBMC Assay (Study 20120283)

Analysis	pCR[a] ABP 980 n/N (%)	Trastuzumab: Excluding Subjects Exposed to Trastuzumab with ADCC Activity Levels ≤ 65%[b] n/N (%)	Trastuzumab: Subjects Exposed to Trastuzumab with ADCC Activity Levels ≤ 65%[c] n/N (%)	RD[d] Estimate	90% CI	95% CI
Assessed by local laboratory						
pCR evaluable population	172/358 (48.0)	116/267 (43.4)	21/71 (29.6)	4.4%	(-2.1%, 11.0%)	(-3.4%, 12.3%)
Assessed by central laboratory						
pCR evaluable population	162/339 (47.8)	114/259 (44.0)	24/71 (33.8)	3.5%	(-3.2%, 10.2%)	(-4.5%, 11.5%)

Biosimilares en EMA:

Datos de Ensayos clínicos necesarios para aprobación

HERZUMA

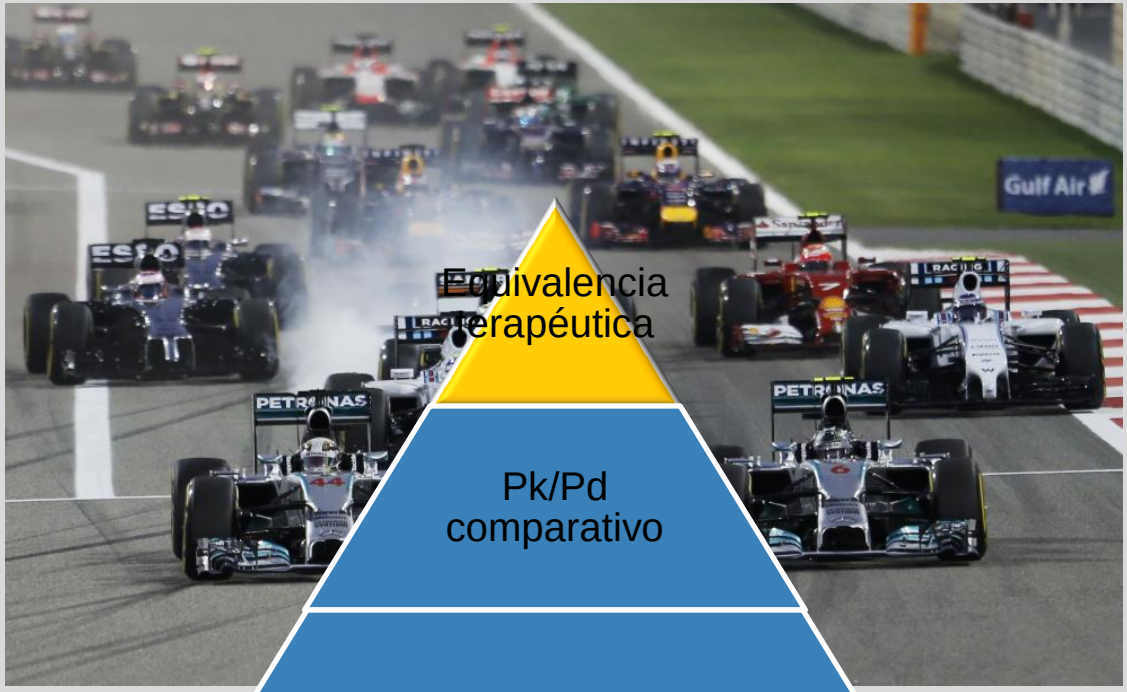
Primary endpoint

The primary endpoint in study CT-P6 3.2 is proportion of patients achieving pCR, defined as the absence of invasive tumour cells in the breast and in axillary lymph nodes regardless of DCIS (tpCR).

Table 21: Proportion of patients achieving pCR after neoadjuvant therapy in Study CT-P6 3.2, ITT Set and PPS

	PPS		ITT	
	CT-P6 (n=248)	Herceptin® (n=2[illegible])	CT-P6 (n=271)	Herceptin® (n=278)
Number of Responders[1] n (%)	116 (46.8)	129 (50.4)	118 (43.5)	131 (47.1)
Number of Non-Responders n (%)	132 ([illegible])	127 (49.6)	153 (56.5)	147 (52.9)
Response Rate (%) (95% CI)[2]	46.8 (40.4 – 53.2)	50.4 (44.1 – 56.7)	43.5 (37.6 – 49.7)	47.1 (41.1 – 53.2)
Treatment Difference (CT-P6 – Herceptin®) (95% CI)[3]	-0.0362 (-0.1238 – 0.0516)		-0.0358 (-0.1198 – 0.0480)	

[1] The number of responders included the patients with pCR of breast and axillary nodes regardless of DCIS.
[2] 95% CI was based on exact binomial approach.
[3] The exact 95% CI for difference was based on unconditional approach.
CI: Confidence interval, ITT: Intent-to-treat, pCR: Pathological complete response, PPS: Per-protocol Set



Equivalencia terapéutica

Pk/Pd comparativo

Preclínica

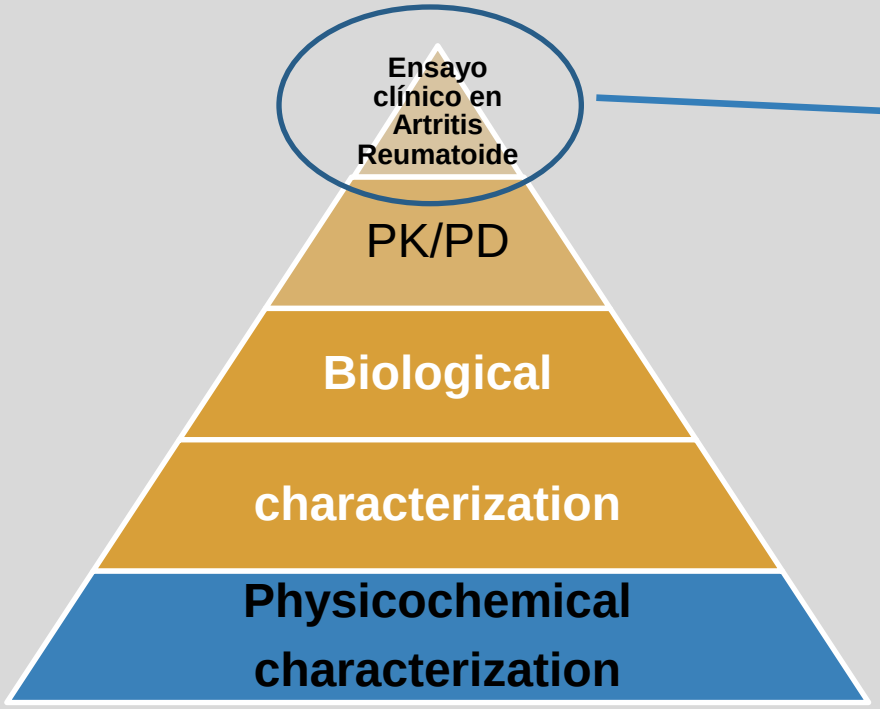
Caracterización biológica

Caracterización Fisicoquímica

Biosimilares

- *¿Qué son?*
- *Demostración de eficacia/seguridad*
- ***Extrapolación de Indicaciones***
- *Farmacovigilancia*
- *Sustitución*

Extrapolación de indicaciones



Infliximab BIOSIMILAR

- Artritis reumatoide
- Enfermedad de Crohn en adultos
- Enfermedad de Crohn en pediatría
- Colitis ulcerosa
- Colitis ulcerosa en pediatría
- Espondilitis anquilosante
- Artritis psoriásica
- Psoriasis

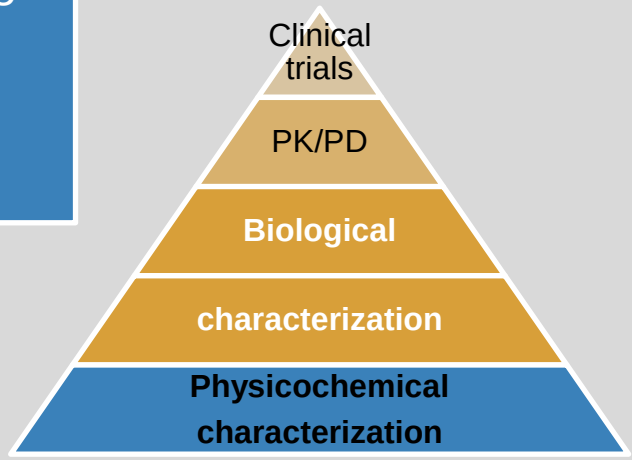
Extrapolación de indicaciones

Está contemplada y se ha realizado

No se aplica de forma sistemática

Es necesario un conocimiento exhaustivo del mecanismo de acción y del propio fármaco

En caso de duda no se realiza



Regarding extrapolation of all indications approved for the reference product Herceptin, scientific evidence are indicating that the mechanism of action of **trastuzumab** is similar in different target conditions in both early and metastatic breast cancer (HER2-positive), as well as HER2-positive gastric cancer. Hence, extrapolation to the non-studied oncology indications is considered acceptable

ABP 215 is convincingly demonstrated to be a biosimilar to the **bevacizumab** reference product is through efficacy comparability studies. The Applicant is claiming the same indications for ABP 215 as granted for the originator Avastin. Since the mechanisms of action are the same, inhibition of tumour vessel growth is expected to be similar across all currently approved cancer indications, extrapolation to all other currently approved indications labelled for the reference product bevacizumab is considered acceptable.

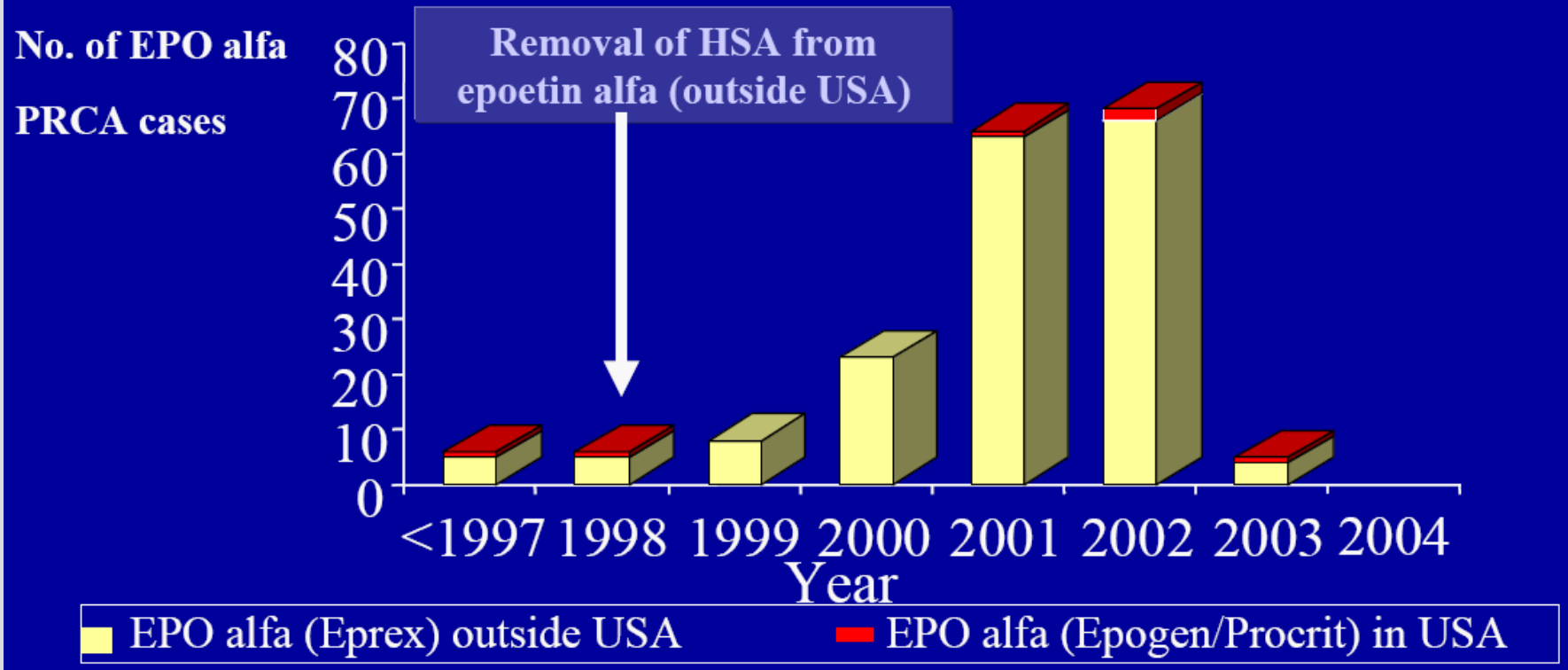
Biosimilarity of CT-P10 and MabThera is considered demonstrated based on the efficacy data. In the pivotal RA trial, efficacy results in terms of DAS28 and ACR were shown to be comparable between CT-P10 and MabThera. In addition, PK data discussed support the extrapolation to the autoimmune indications MPA/GPA.

The objectives of study CT-P10 3.3 were to demonstrate similarity in pharmacokinetics and non-inferiority in efficacy of CT-P10 to Rituxan as primary endpoints when coadministered with CVP in patients with advanced FL; these objectives have been met and furthermore, extrapolation in the context of NHL and CLL indications is acceptable.

Biosimilares

- *¿Qué son?*
- *Demostración de eficacia/seguridad*
- *Extrapolación de Indicaciones*
- ***Farmacovigilancia***
- *Sustitución*

EPO alfa PRCA cases



- Epoetin α formulation in US still contains HSA
  - No increase in EPO-associated PRCA in USA

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

agencia española de medicamentos y productos sanitarios

Lecciones aprendidas

✓El desarrollo de anticuerpos **no se puede anticipar** (reacciones muy raras). Con incidencias de 1-3/100.000 no es posible detectarlo pre-autorización en ensayos clínicos.

✓Cuando son detectados es demasiado tarde.

✓Sólo un “Risk Management Plan” sólido es capaz de ver este tipo de efectos.

✓De asuntos como este surgen las disposiciones sobre especial vigilancia de la Directiva 2010/84 de Farmacovigilancia.

Farmacovigilancia

Medicamentos sujetos a un seguimiento adicional

Es importante que el refuerzo del sistema de farmacovigilancia no conduzca a la concesión prematura de autorizaciones de comercialización. No obstante, algunos medicamentos se autorizan a reserva de un seguimiento adicional. Entre ellos se encuentran todos los **medicamentos con un nuevo principio activo** y los **medicamentos biológicos, incluidos los biosimilares**, que en farmacovigilancia son prioritarios.

Los medicamentos sujetos a un seguimiento adicional deben identificarse mediante un **símbolo negro** y una frase explicativa estándar adecuada en el resumen de las características del producto y en y en el prospecto.

Real Decreto 577/2013, de 26 de julio, por el que se regula la farmacovigilancia de medicamentos de uso humano.

Biosimilares

- *¿Qué son?*
- *Demostración de eficacia/seguridad*
- *Extrapolación de Indicaciones*
- *Farmacovigilancia*
- ***Sustitución***

SUSTITUCION

La evaluación no garantiza la intercambiabilidad

- ✓Nuestro reglamento exige una relación beneficio/riesgo positiva
- ✓Metodológicamente esa demostración es de elevada complejidad
- ✓Tampoco se evalua en el resto de medicamentos pero se intercambia
- ✓Actuar con precaución (conocimiento del médico y del paciente)

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GRACIAS