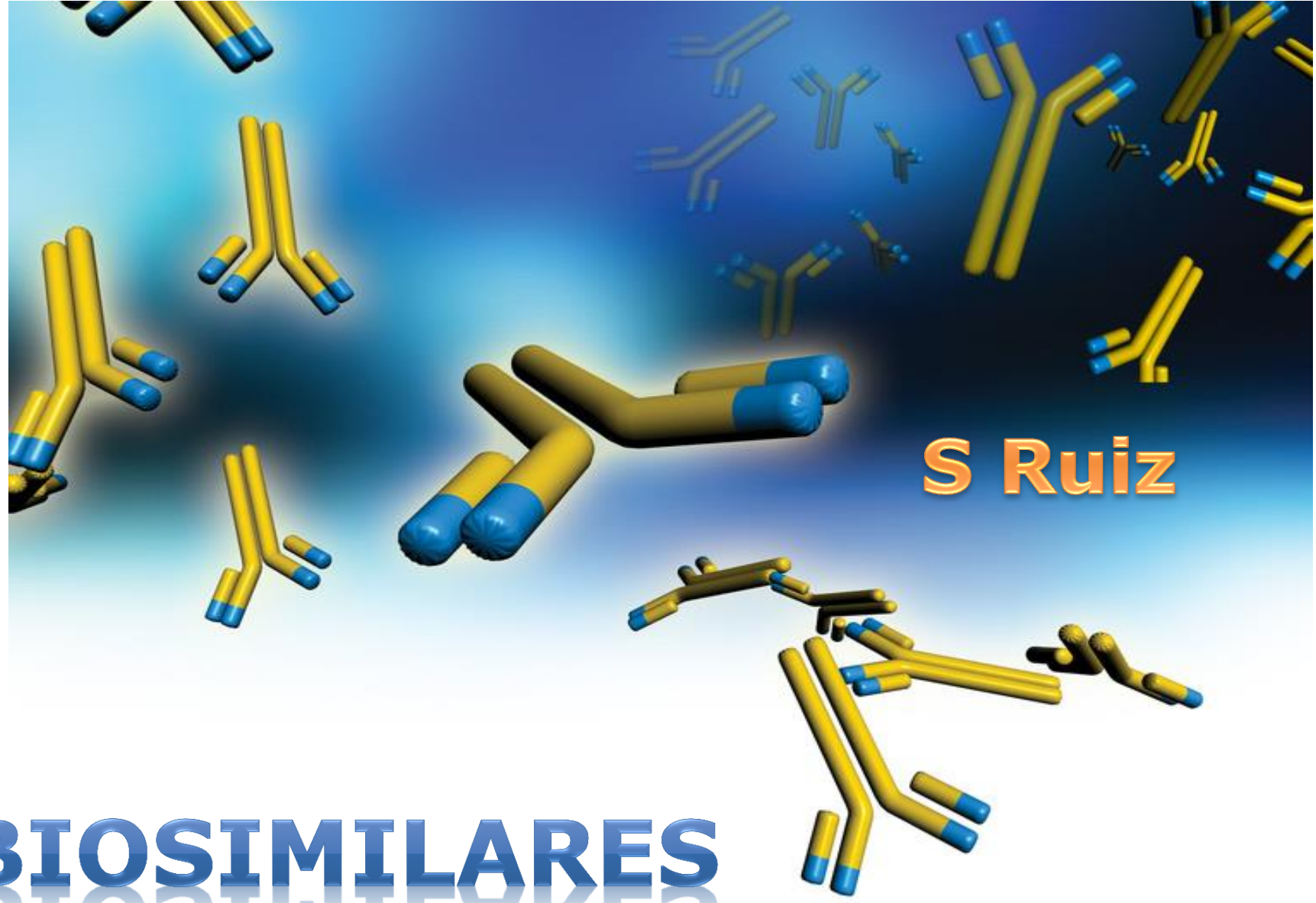


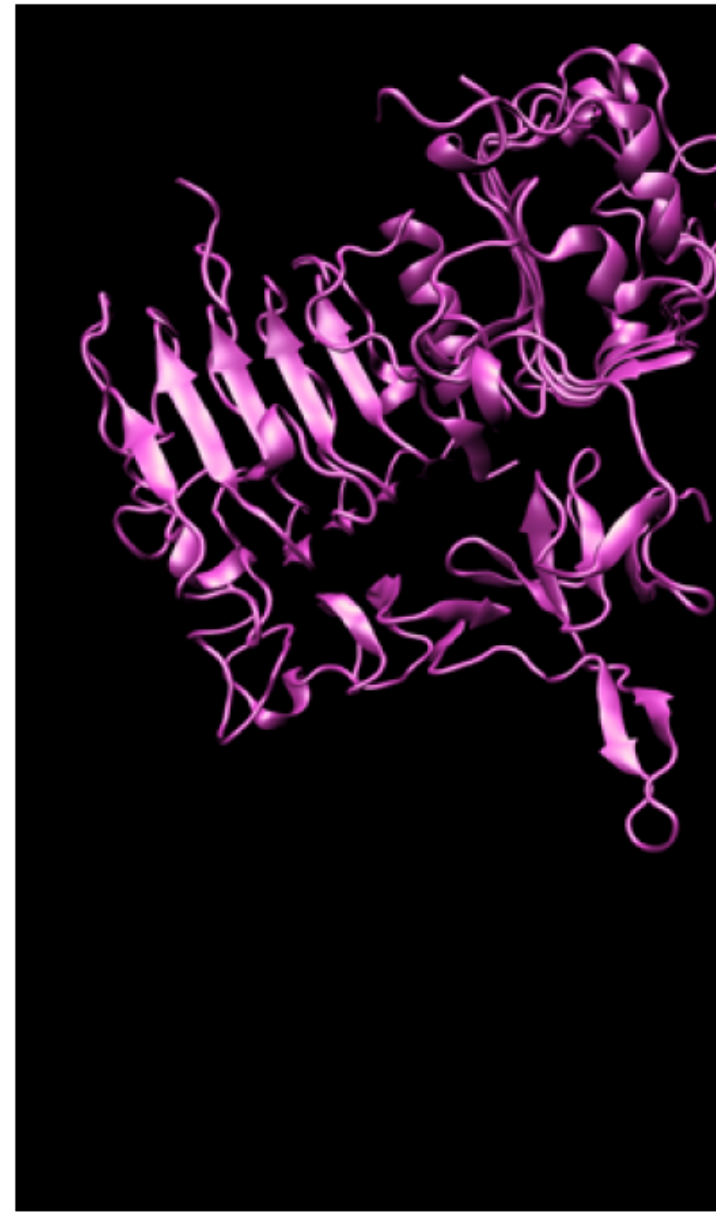

# BIOSIMILARES

SERPE 27-11-2015

BMJ | 19 SEPTEMBER 2009 | VOLUME 339

# Biological therapies: how can we afford them?

Demand for biological drugs is putting pressure on health budgets. **Christopher Kelly** and **Fraz Mir** examine why they are so expensive and what can be done to increase access



The success of biopharmaceuticals is producing a growing problem for public healthcare services worldwide. Newer biological therapies offer fresh hope for the treatment of many serious diseases but are much more expensive than conventional drugs. Clinicians are increasingly finding themselves torn between offering new treatments to patients and respecting the financial restrictions imposed by healthcare authorities on the basis of cost effectiveness.

In the UK, the NHS has been under pressures of cuts in public spending, to survive in the current financial climate. We examine the reasons for the high costs and the possibilities for reducing them.

## Revolutionary drug treatment

Biological therapies are generally derived from living material (human, animal, or micro-organism) and have a highly complex chemical structure. Many fundamental differences exist between biological drugs and traditional "small molecule" drugs (table 1).[2]

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

06/10/2015

| Medicine Name | Active Substance | Marketing Authorisation Holder |
|---|---|---|
| Abasaglar (previously Abasria) | insulin glargine | Eli Lilly Regional Operations GmbH |
| Abseamed | epoetin alfa | Medice Arzneimittel Pütter GmbH & Co. KG |
| Accofil | filgrastim | Accord Healthcare Ltd |
| Alpheon | rHuIFN alfa | BioPartners GmbH |
| Bemfola | follitropin alfa | Finox Biotech AG |
| Binocrit | epoetin alfa | Sandoz GmbH |
| Biograstim | filgrastim | AbZ-Pharma GmbH |
| Epoetin Alfa Hexal | epoetin alfa | Hexal AG |
| Filgrastim Hexal | filgrastim | Hexal AG |
| Filgrastim ratiopharm | filgrastim | Ratiopharm GmbH |
| Grastofil | filgrastim | Apotex Europe BV |
| Inflectra | infliximab | Hospira UK Limited |
| Nivestim | filgrastim | Hospira UK Ltd |
| Omnitrope | somatropin | Sandoz GmbH |
| Ovaleap | follitropin alfa | Teva Pharma B.V. |
| Ratiograstim | filgrastim | Ratiopharm GmbH |
| Remsima | infliximab | Celltrion Healthcare Hungary Kft. |
| Retacrit | epoetin zeta | Hospira UK Limited |
| Silapo | epoetin zeta | Stada Arzneimittel AG |
| Tevagrastim | filgrastim | Teva GmbH |
| Valtropin | somatropin | BioPartners GmbH |
| Zarzio | filgrastim | Sandoz GmbH |

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Publications

# Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 16-19 November 2015



News

20/11/2015

## Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 16-19 November 2015

**Ten medicines, including a first-in-class orphan medicine for narcolepsy, recommended for authorisation in the EU**

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended ten medicines for marketing authorisation at its November 2015 meeting.

The CHMP recommended granting a marketing authorisation for **Wakix** (pitolisant) for the treatment of narcolepsy. Narcolepsy is a rare, long-term sleep disorder which affects the brain's ability to regulate the normal sleep-wake cycle, and may occur with or without cataplexy (sudden severe muscle weakness or loss of muscle control). Wakix, a first-in-class medicine, has an orphan designation. For more information, please see the press release in the grid below.

The CHMP recommended granting a marketing authorisation for two blood cancer medicines: **Oncaspar** (pegaspargase) and **Spectrila** (asparaginase), both for the treatment of acute lymphoblastic leukaemia. Spectrila has an orphan designation.

**Benepali** (etanercept), a biosimilar, received a positive opinion for the treatment of rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis and plaque psoriasis.

**Briviact** (brivaracetam) was recommended for marketing authorisation by the Committee for the treatment of partial-onset epilepsy seizures.

The CHMP recommended granting a marketing authorisation to **Episalvan** for the treatment of partial thickness wounds in adults. The active substance of Episalvan is birch bark extract.

**Related information**
- Cimzia: EPAR
- Zutectra: EPAR
- Human papillomavirus vaccines: Article 20 procedures
- Cimzia: Pending EC decision
- Spectrila: Pending EC decision
- Episalvan: Pending EC decision
- Lopinavir/Ritonavir Mylan: Pending EC decision
- Solumarv: Pending EC decision
- Pemetrexed Actavis: Pending EC decision
- Zutectra: Pending EC decision
- Pemetrexed Accord: Pending EC decision
- Oncaspar: Pending EC decision
- Wakix: Pending EC decision
- Benepali: Pending EC decision
- Briviact: Pending EC decision

**Related content**
- Narcolepsy treatment recommended for approval (20/11/2015)
- HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS

reference


biosimilar


QSE
reference
biosimilar
comp
studies

# Biosimilars in the EU

## general considerations

- Marketing authorization through the centralized procedure (biotechnological products)
- Same posology and route of administration as the reference product
- A single reference medicinal product (marketed in the EEA) should be used as the comparator throughout the comparability programme (Q,S,E).

# Biosimilars in the EU

## general considerations

- A stepwise approach is recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation.
- The extent and nature of the nonclinical in vivo studies and clinical studies to be performed depend on the level of evidence obtained in the previous step(s).
- **Pharmacovigilance system and risk management plan**

**Directives 2003/63 - 2004/27**

**Overarching**

Guideline on Similar Biological Medicinal Products

**Quality**

Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues

**Nonclinical & Clinical**

Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical & Clinical Issues

**Annexes**

- EPO
- G-CSF
- Insulin
- IFNα
- IFNβ
- hGH
- FSH
- LMWH
- MAbs

European Medicines Agency
*Evaluation of Medicines for Human Use*

CHMP/437/04
London, 30 October 2005

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

# GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS

| | |
|---|---|
| **DISCUSSION AT THE CHMP** | JUNE 2004 |
| **ADOPTION BY CHMP** | NOVEMBER 2004 |
| **RELEASE FOR CONSULTATION** | NOVEMBER 2004 |
| **DEADLINE FOR COMMENTS** | FEBRUARY 2005 |
| **DISCUSSION AT WORKING PARTIES** | JUNE 2005 |
| **ADOPTION BY CHMP** | SEPTEMBER 2005 |
| **DATE FOR COMING INTO EFFECT** | 30 OCTOBER 2005 |

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 Medicinal Products Working Party and Biologics Working Party | March 2013 |
| Adopted by CHMP for release for consultation | 25 April 2013 |
| Start of public consultation | 30 April 2013 |
| End of consultation (deadline for comments) | 31 October 2013 |
| Revised draft agreed by Biosimilar Medicinal Products Working Party and Biologics Working Party | July 2014 |
| Adoption by CHMP | 23 October 2014 |
| Date for coming into effect | 30 April 2015* |

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2015

- The active substance of a biosimilar must be similar, in molecular and biological terms, to the active substance of the reference medicinal product. For example, for an active substance that is a protein, the amino acid sequence is expected to be the same.
- The posology and route of administration of the biosimilar must be the same as those of the reference medicinal product.
- Deviations from the reference product as regards strength, pharmaceutical form, formulation, excipients or presentation require justification. If needed, additional data should be provided. Any difference should not compromise safety.
- Intended changes to improve efficacy (e.g. glycooptimisation) are not compatible with the biosimilarity approach. However, differences that could have an advantage as regards safety (for instance lower levels of impurities or lower immunogenicity) should be addressed, but may not preclude biosimilarity.

### *3.3. Principles of establishing biosimilarity*

The guiding principle of a biosimilar development programme is to establish similarity between the biosimilar and the reference product by the best possible means, ensuring that the previously proven safety and efficacy of the reference medicinal product also applies to the biosimilar.

A biosimilar should be highly similar to the reference medicinal product in physicochemical and biological terms. Any observed differences have to be duly justified with regard to their potential impact on safety and efficacy.

A stepwise approach is normally recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation. The extent and nature of the non-clinical *in vivo* studies and clinical studies to be performed depend on the level of evidence obtained in the previous step(s) including the robustness of the physicochemical, biological and non-clinical *in vitro* data.

The ultimate goal of the biosimilar comparability exercise is to exclude any relevant differences between the biosimilar and the reference medicinal product. Therefore, studies should be sensitive enough with regard to design, conduct, endpoints and/or population to detect such differences.

# Module 3 Quality

Same as for any other biological

+

Comparability studies vs the reference product



European Medicines Agency

June 2005
CPMP/ICH/5721/03

**ICH Topic Q 5 E**
**Comparability of Biotechnological/Biological Products**

**Step 5**

# NOTE FOR GUIDANCE ON BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS

(CPMP/ICH/5721/03)

| | |
|---|---|
| TRANSMISSION TO CHMP | November 2003 |
| TRANSMISSION TO INTERESTED PARTIES | November 2003 |
| DEADLINE FOR COMMENTS | May 2004 |
| FINAL APPROVAL BY CHMP | December 2004 |
| DATE FOR COMING INTO OPERATION | June 2005 |

European Medicines Agency

June 2005
CPMP/ICH/5721/03

# ICH Topic Q 5 E
# Comparability of Biotechnological/Biological Products

## 1.4 *General Principles*

The goal of the comparability exercise is to ensure the quality, safety and efficacy of drug product produced by a changed manufacturing process, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes.

The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.

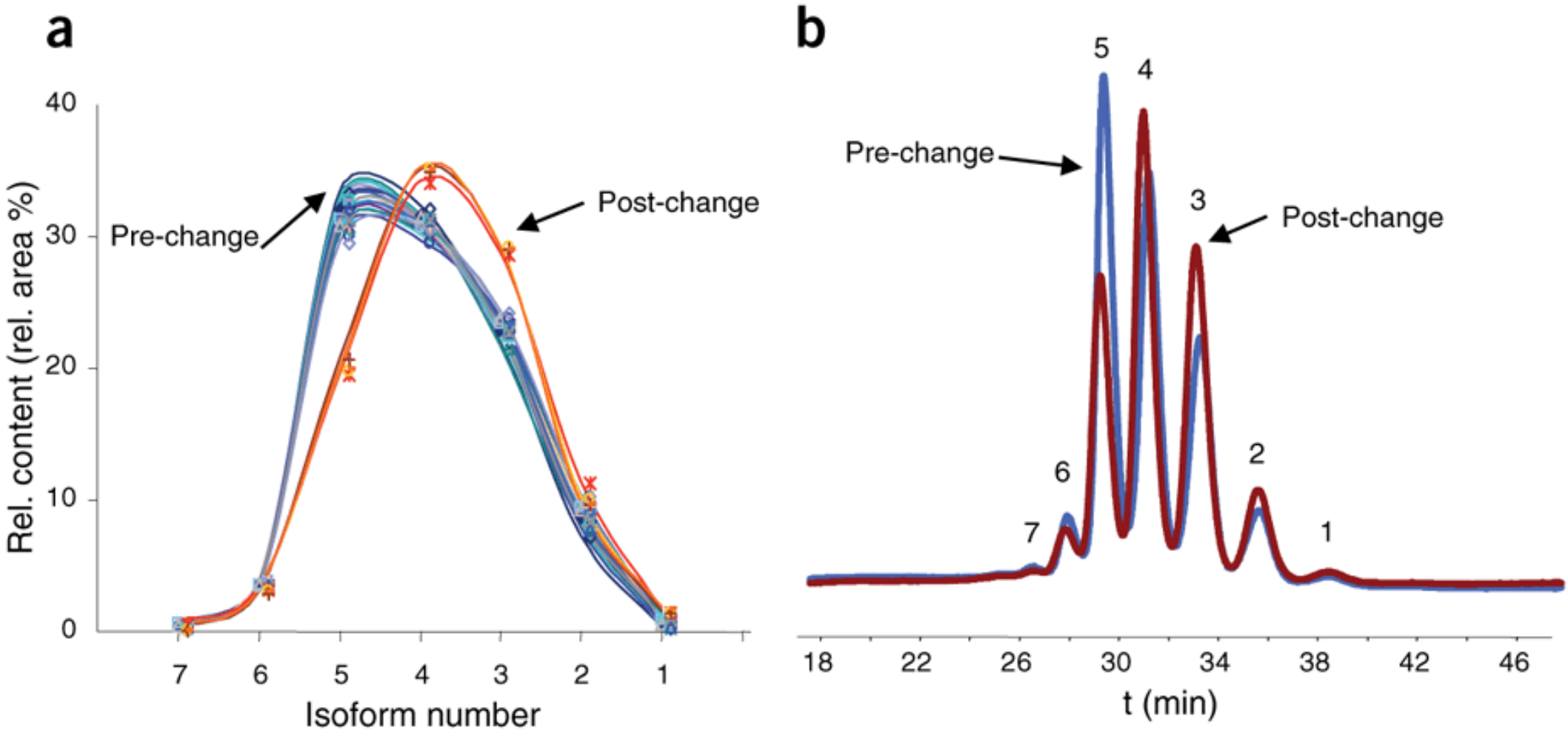



**Figure 1** Comparison of the pre- and post-change Aranesp batches measured by capillary zone electrophoresis. (**a**) Relative content of the individual isoforms of the pre-change ($n = 18$) and the post-change ($n = 4$) batches. (**b**) Representative electropherograms; peaks are labeled with the isoform number.

© 2011 Nature Amer

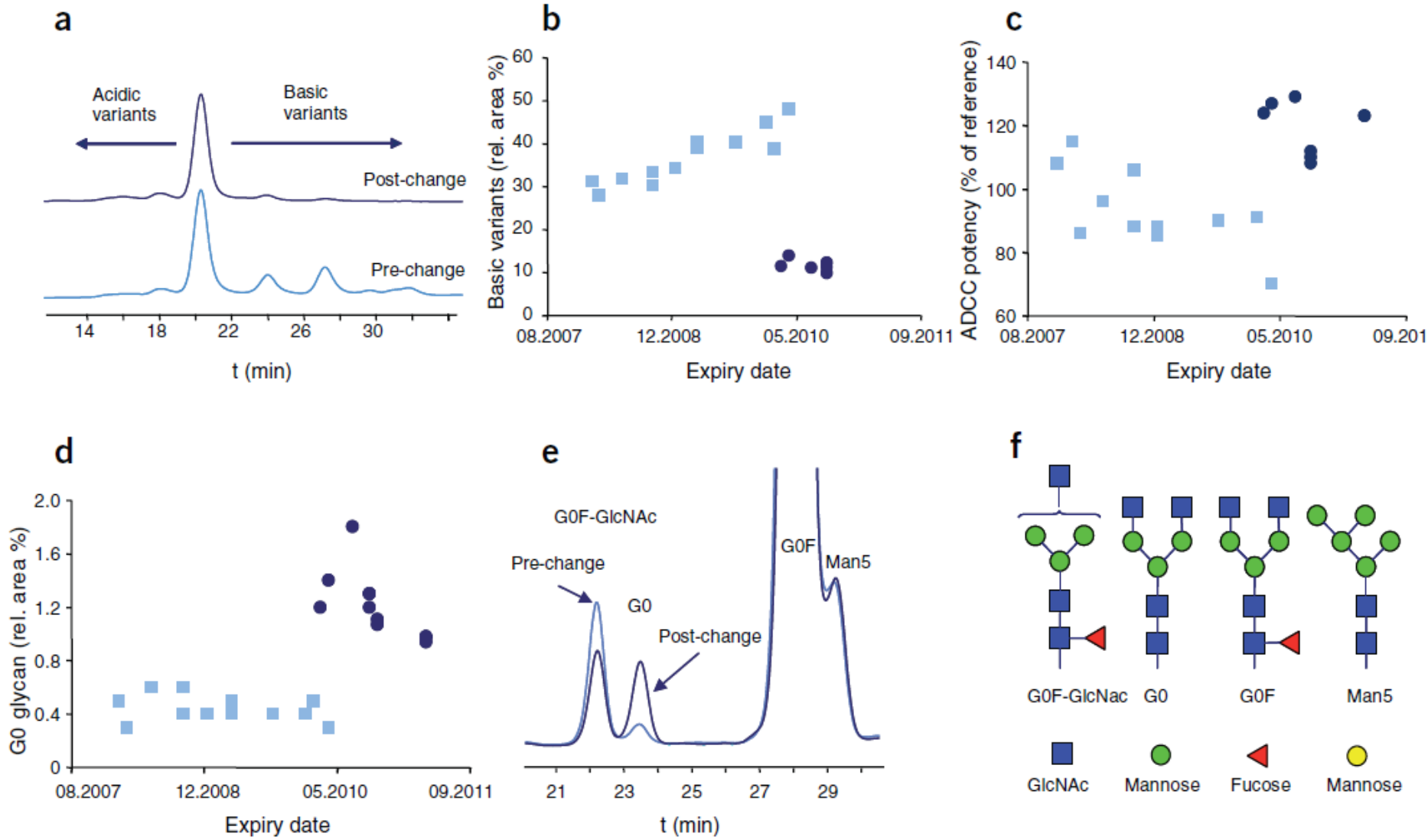
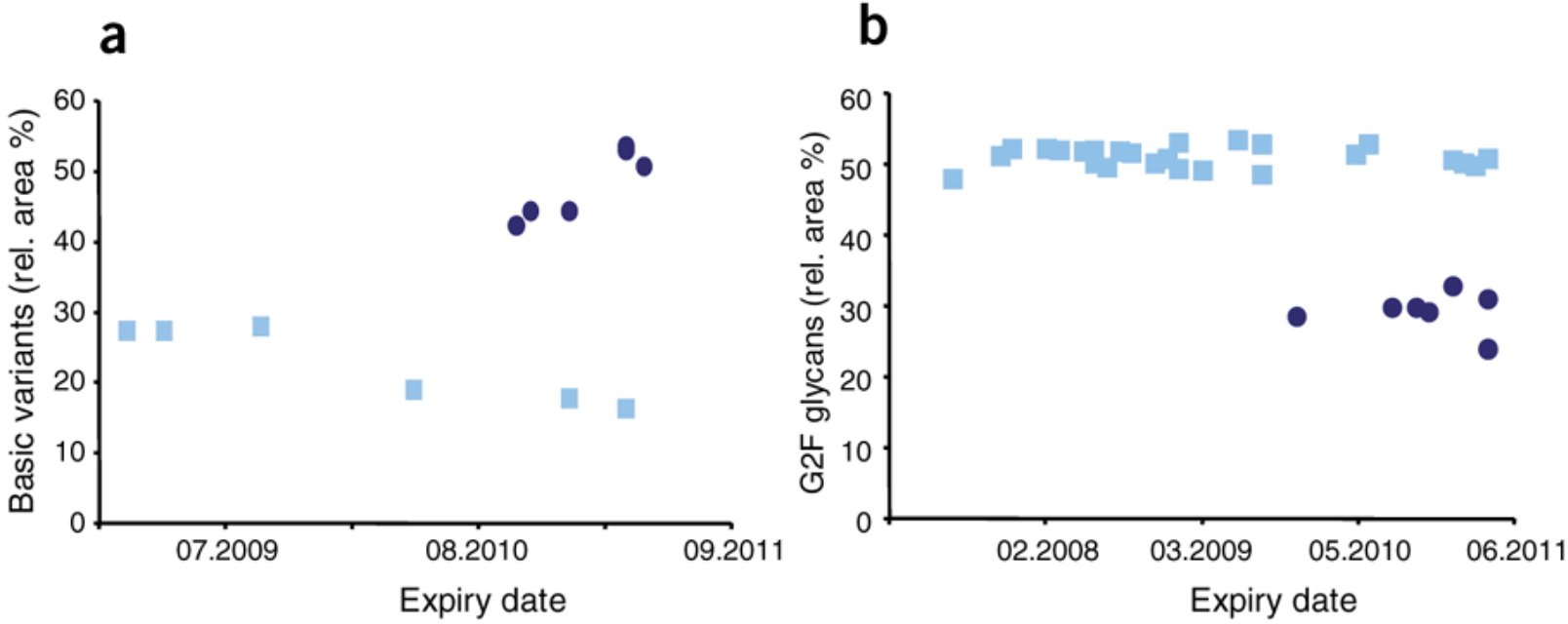
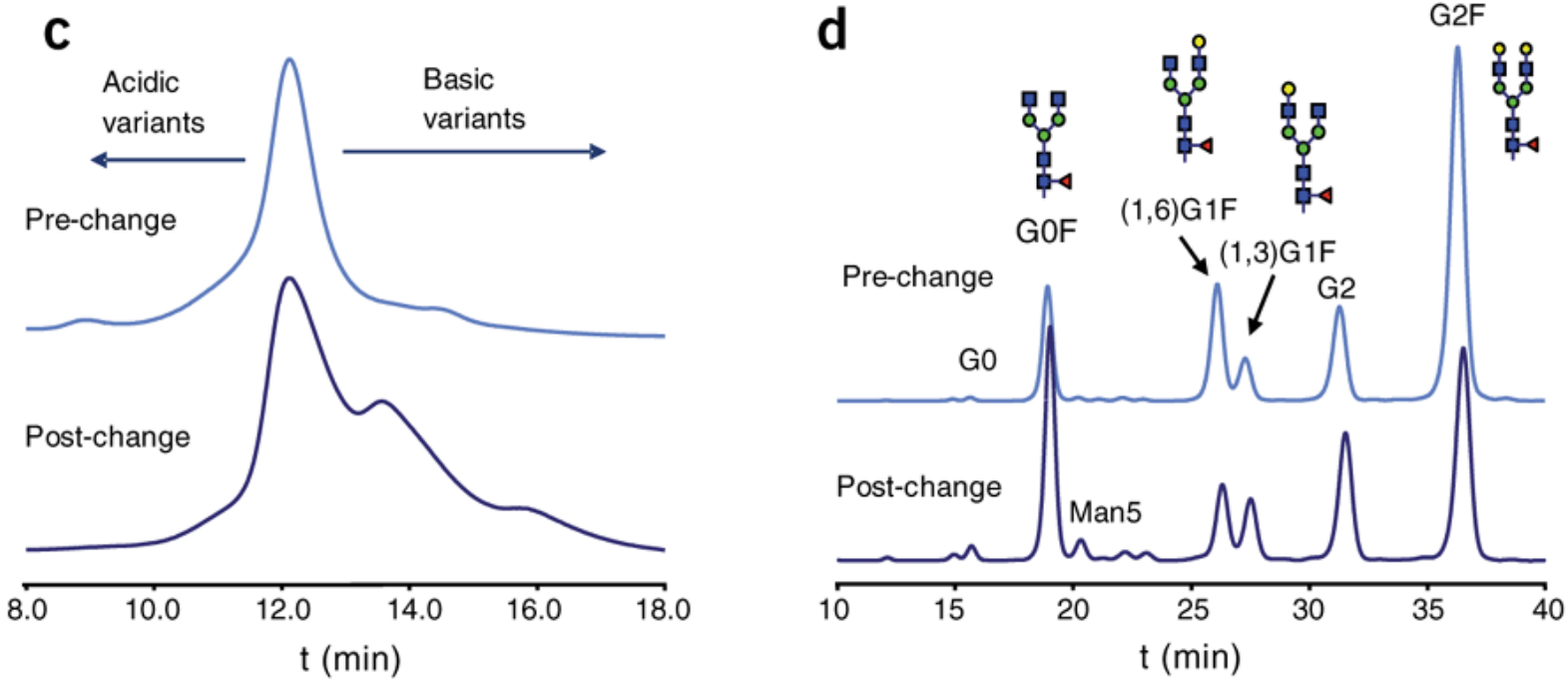



**Figure 2** Comparison of the different pre- and post-change batches of Rituxan/Mabthera. (**a**) Exemplary CEX chromatograms. (**b**) Amount of basic variants of the pre-change ($n = 12$) and post-change ($n = 6$) batches as measured by CEX. (**c**) ADCC potency of the pre-change ($n = 11$) and post-change ($n = 8$) batches. (**d**) Relative amount of the G0 glycan of the pre-change ($n = 13$) and post-change ($n = 11$) batches. (**e**) Exemplary glycan mapping chromatogram (**f**) Glycan legend.

# Enbrel


a
Basic variants (rel. area %)
60
50
40
30
20
10
0
07.2009
08.2010
09.2011
Expiry date
b
G2F glycans (rel. area %)
60
50
40
30
20
10
0
02.2008
03.2009
05.2010
06.2011
Expiry date


c
Acidic variants
Basic variants
Pre-change
Post-change
8.0
10.0
12.0
14.0
16.0
18.0
t (min)
d
G2F
G0F
(1,6)G1F
(1,3)G1F
G2
Pre-change
G0
Post-change
Man5
10
15
20
25
30
35
40
t (min)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 May 2014
EMA/CHMP/BWP/247713/2012
Committee for Medicinal Products for Human Use (CHMP)

# Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)

| | |
|---|---|
| Draft Agreed by BWP | April 2012 |
| Adoption by CHMP for release for consultation | 24 May 2012 |
| Start of public consultation | 31 May 2012 |
| End of consultation (deadline for comments) | 30 November 2012 |
| Revised draft agreed by BMWP and BWP | April 2014 |
| Adoption by CHMP | 22 May 2014 |
| Date for coming into effect | 1 December 2014 |

This guideline replaces 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (EMEA/CHMP/BWP/49348/2005)'

# physicochemical properties

Evaluation of physicochemical parameters;

- composition
- physical properties
- primary and higher order structures
- structural identification of product-related substances and impurities

**Table 1 Physicochemical characterization tests**

| Parameter | Analytical tests |
|---|---|
| Primary structure | Amino acid composition analysis, MS, N/C-terminal sequencing, TPM and sequencing/MS |
| Higher order structure | CD, NMR, immunoreactivity with conformational-dependent antibodies, TPM/MS, biological assays |
| Size | AUC, field flow fractionation, MALDI-TOF MS, LC-ESI, SDS-PAGE, SEC-HPLC |
| Charge | CE, IEC, IEF |
| Hydrophobicity | HIC-HPLC, RP-HPLC |
| Immunoreactivity | Immunoprecipitation, western blot analysis |
| *For glycosylated products* | |
| Glycosylation pattern/sequence | CE, HPAEC-PAD, LC-ESI, MALDI-TOF MS, RP-HPLC |
| Identification of glycosylation sites | TPM/MS |

AUC, analytical ultracentrifugation; CD, circular dichroism; CE, capillary electrophoresis; ESI, electrospray ionization mass spectrometry; HPAEC-PAD, high pH anion exchange chromatography with pulsed amperometric detection; HIC, hydrophobic interaction column; IEC, ion-exchange chromatography; IEF, isoelectric focusing gel electrophoresis; LC, liquid chromatography; MS, mass spectrometry; MALDI-TOF MS, matrix-assisted laser desorption/ionization-time of flight; NMR, nuclear magnetic resonance; RP-HPLC, reversed phase high-performance liquid chromatography; SEC, size exclusion chromatography; TPM, trypsin peptide mapping.

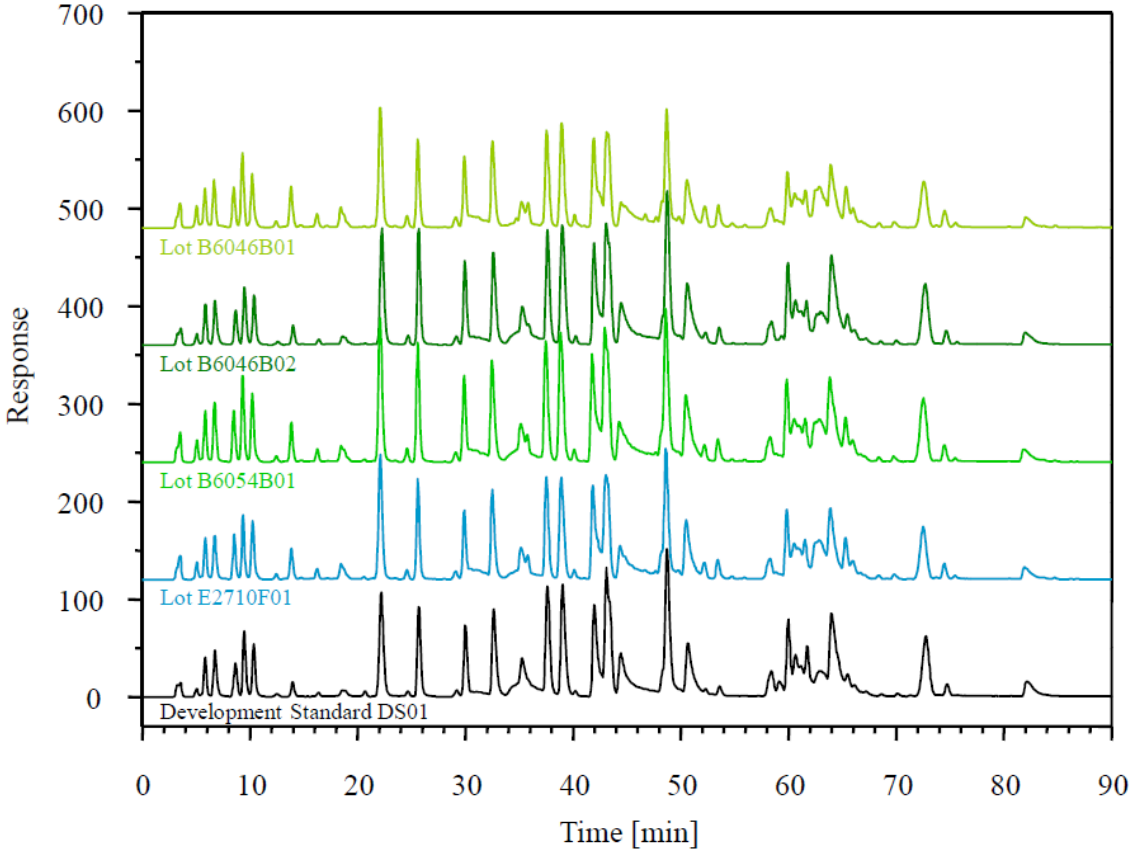
# biological activity

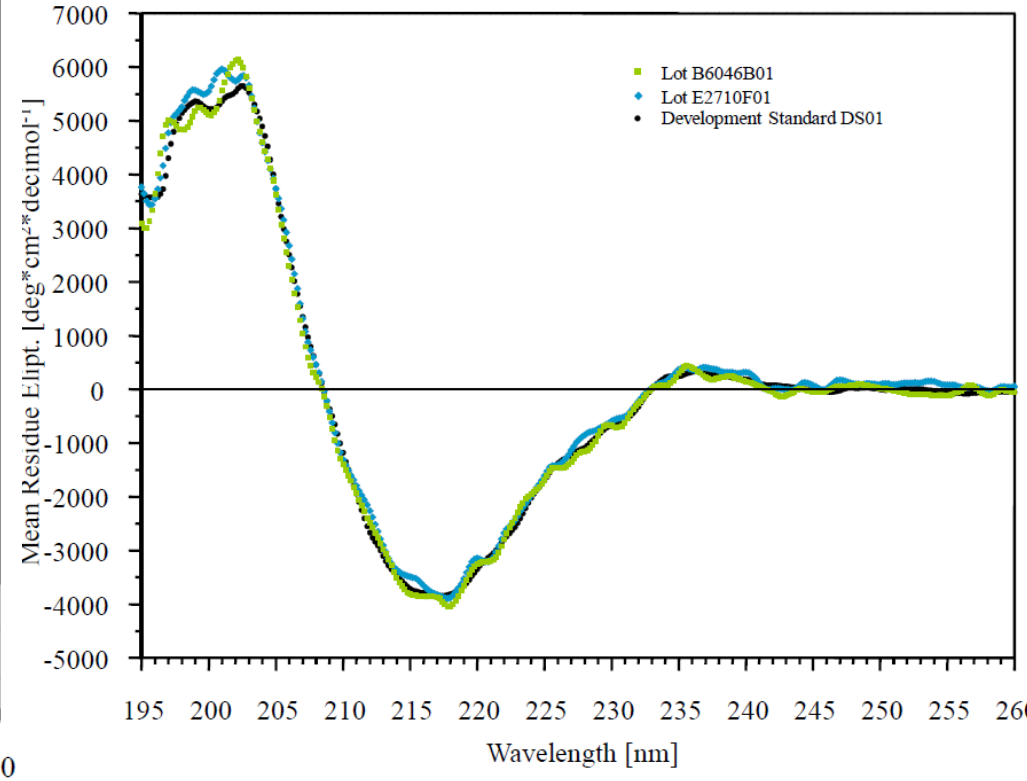
**Different approaches** to measure the biological activity should be considered (according to the biological properties of the product).

# IFN-beta

## FUNCTIONAL ANALYSIS

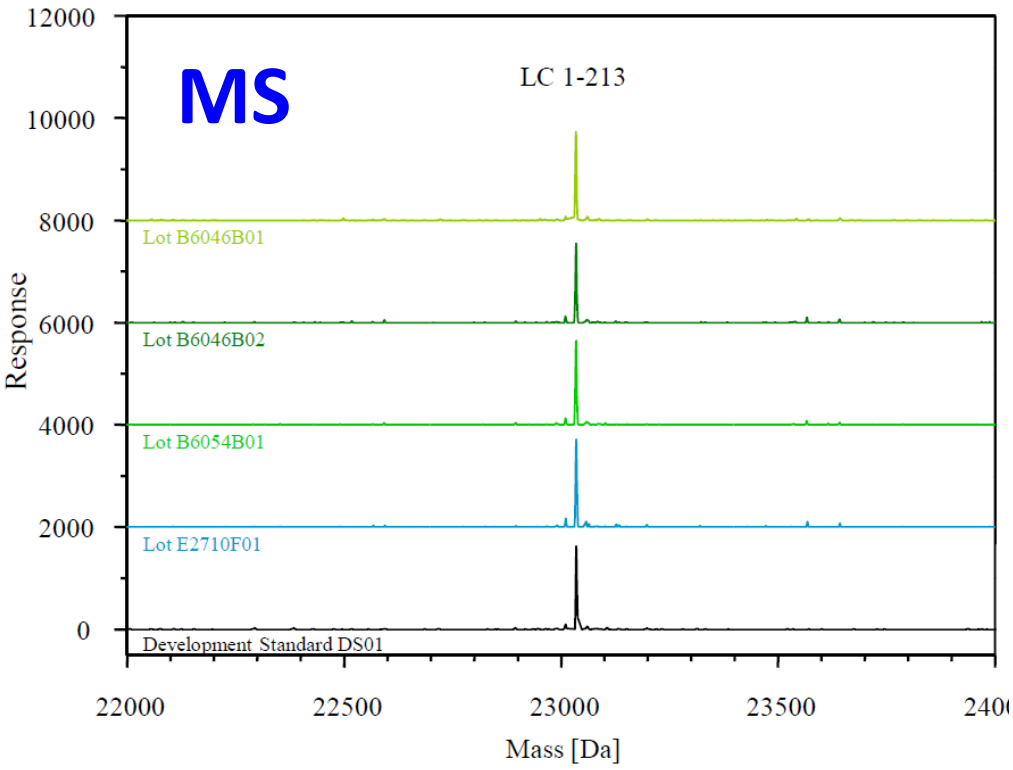
- antiviral activity
- antiproliferative activities (using different cell lines)
- immunomodulatory activities
- receptor binding
- formation of activated IFN stimulated gene factor complex
- IFN-beta inducible mRNAs

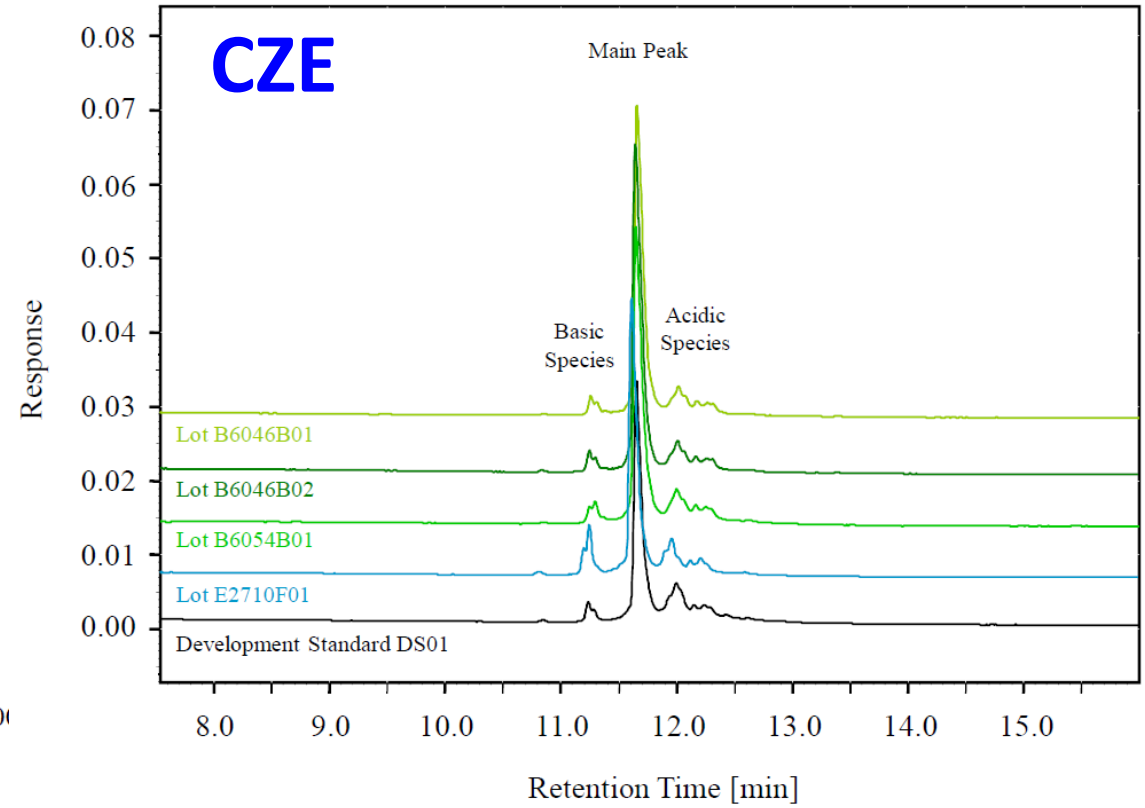


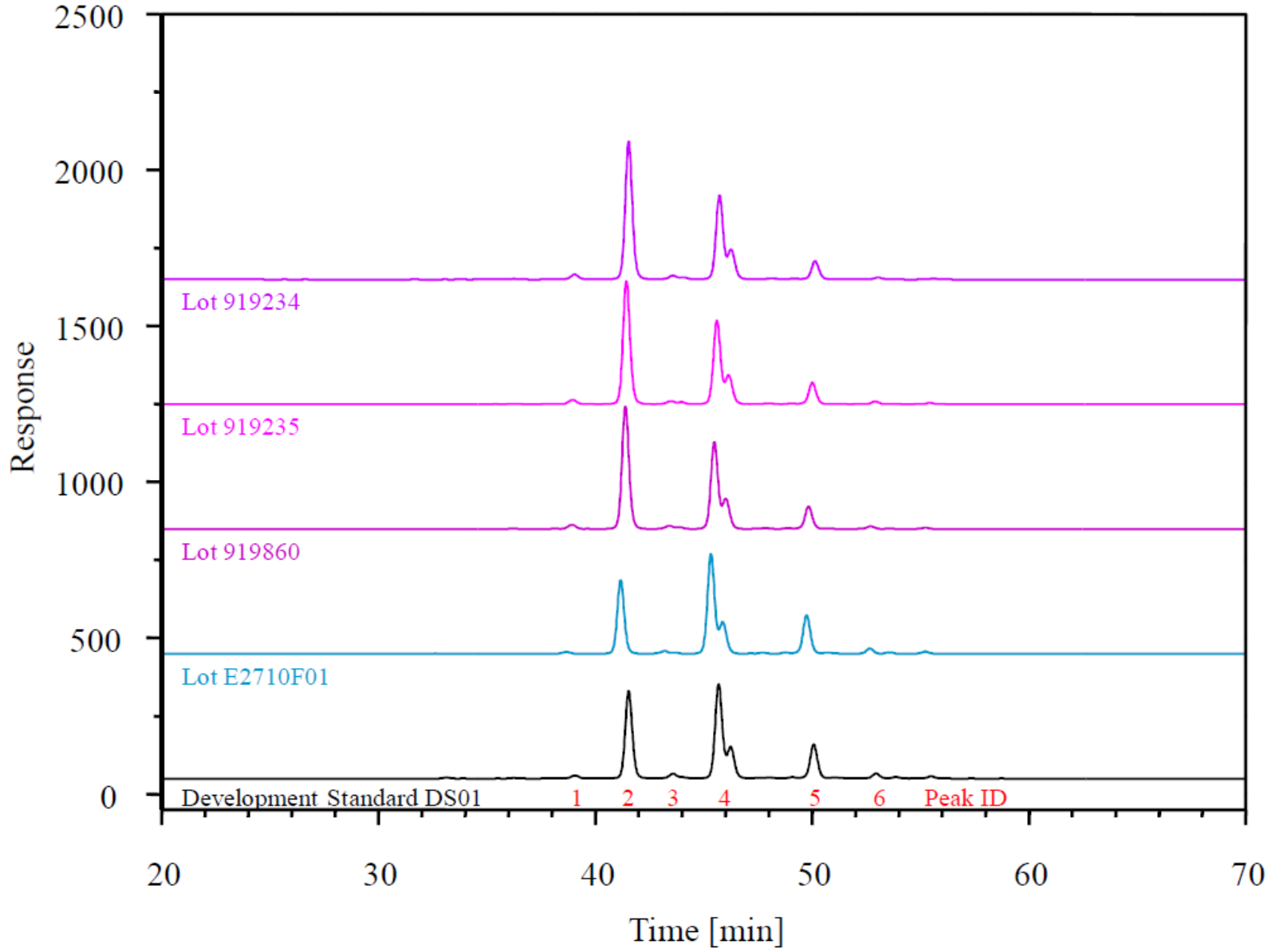




**TRYPTIC MAP**

**CD spectra**


MS
LC 1-213
Response
Mass [Da]
Lot B6046B01
Lot B6046B02
Lot B6054B01
Lot E2710F01
Development Standard DS01
12000
10000
8000
6000
4000
2000
0
22000
22500
23000
23500


CZE
Main Peak
Basic Species
Acidic Species
Response
Retention Time [min]
Lot B6046B01
Lot B6046B02
Lot B6054B01
Lot E2710F01
Development Standard DS01
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
8.0
9.0
10.0
11.0
12.0
13.0
14.0
15.0




**Oligosaccharide map**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 December 2014
EMEA/CHMP/BMWP/42832/2005 Rev1
Committee for Medicinal Products for Human Use (CHMP)

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

| | |
|---|---|
| Draft agreed by Biosimilar Medicinal Products Working Party (BMWP) | April 2013 |
| Adopted by CHMP for release for consultation | 30 May 2013 |
| Start of public consultation | 03 June 2013 |
| End of consultation (deadline for comments) | 30 November 2013 |
| Agreed by Biosimilar Medicinal Products Working Party (BMWP) | October 2014 |
| Adopted by CHMP | 18 December 2014 |
| Date for coming into effect | 01 July 2015 |

This guideline replaces 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues' (EMEA/CHMP/BMWP/42832/2005).

# Executive summary

The *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues* (EMEA/CHMP/BMWP/42832/05 Rev.1) lays down the non-clinical and clinical requirements for a similar biological medicinal product ("biosimilar").

The non-clinical section addresses the pharmaco-toxicological assessment. The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, and efficacy studies. The section on clinical safety and pharmacovigilance addresses clinical safety studies, including immunogenicity, as well as the risk management plan.

The current revision covers the following topics: a stepwise approach for the design of non-clinical studies; the use of pharmacodynamic markers; study design, choice of appropriate patient population and choice of surrogate and clinical endpoints in efficacy trials; clinical safety (including design of immunogenicity studies), risk management plan, and pharmacovigilance, and extrapolation of safety and efficacy. The guideline recommends a stepwise conduct of non-clinical and clinical studies.

# NON-CLINICAL STUDIES

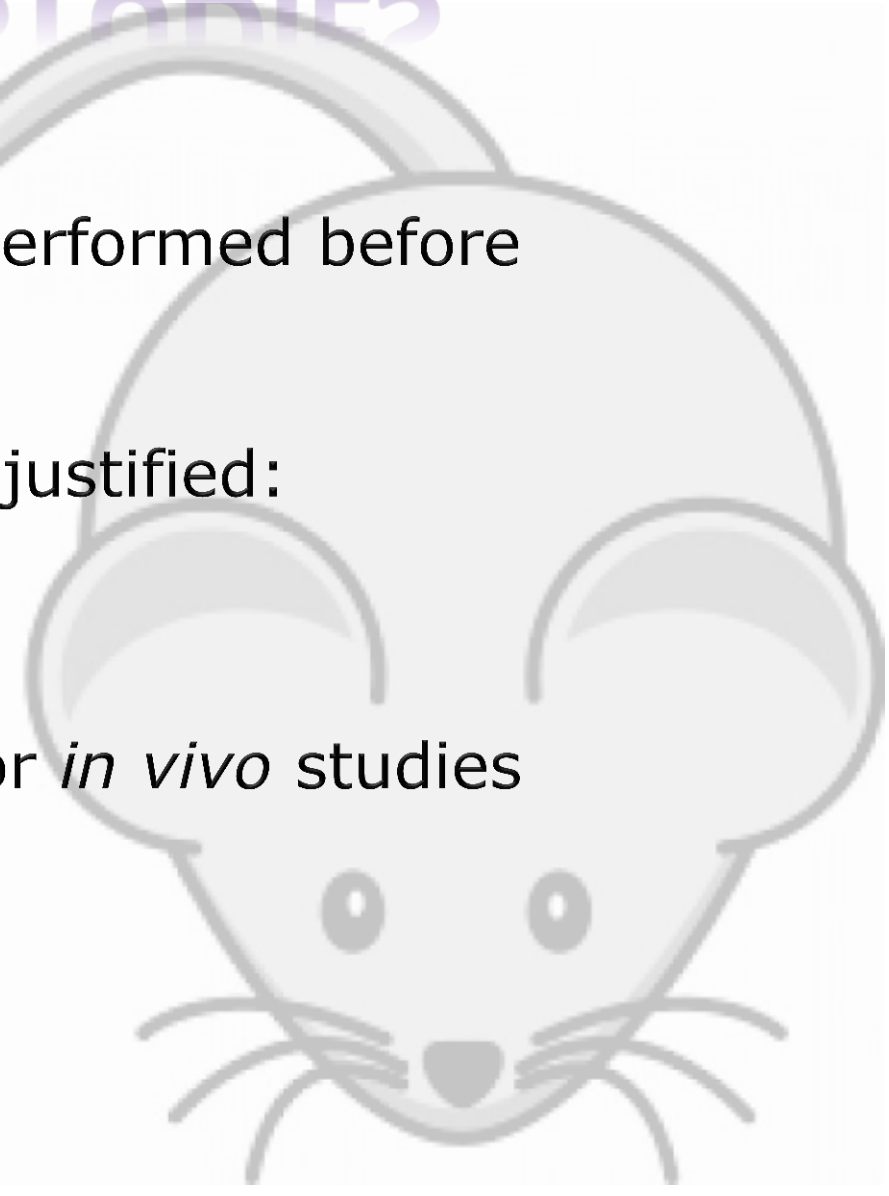
Non-clinical studies should be performed before initiating clinical trials.

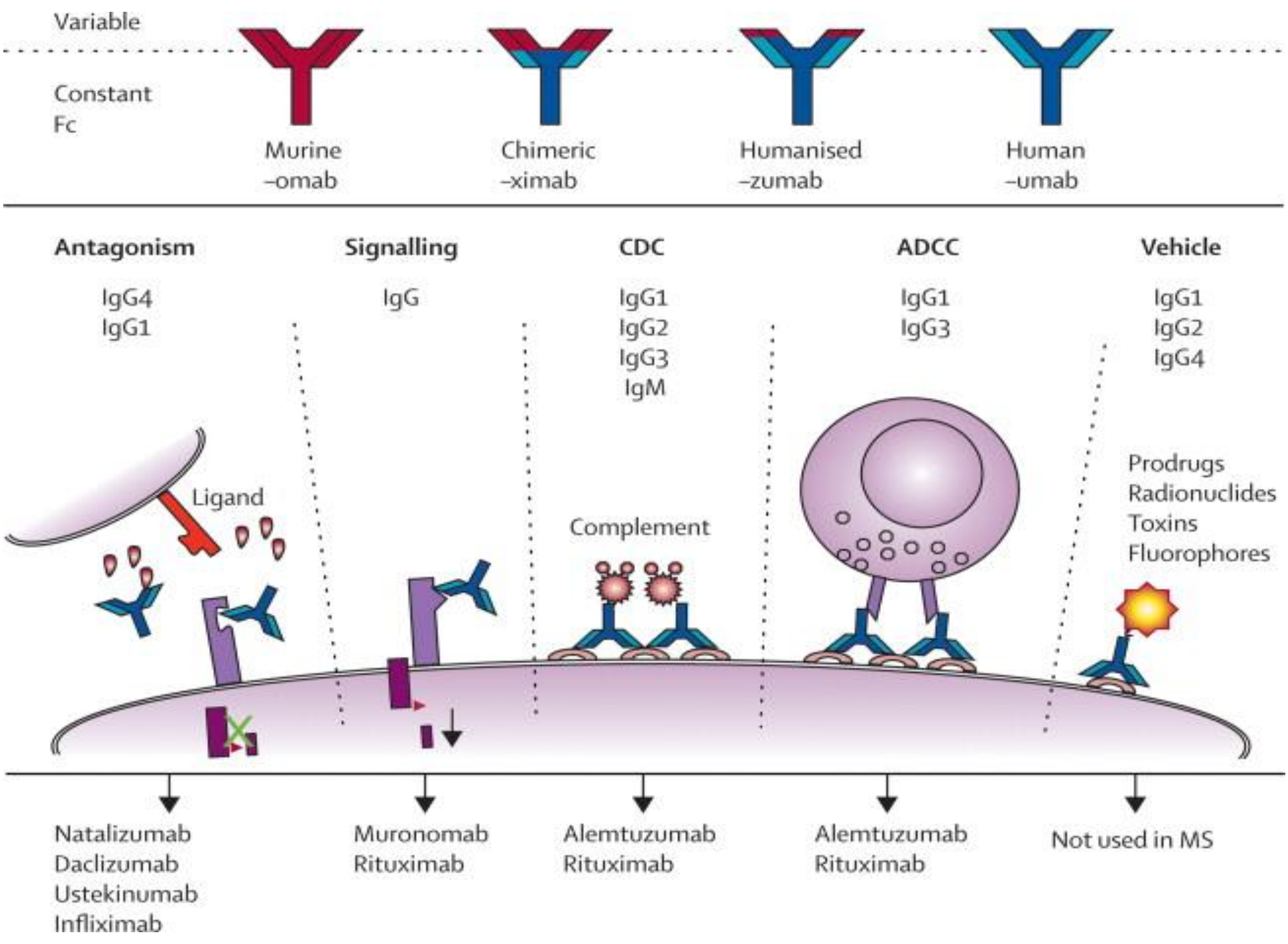
Step-wise approach; should be justified:

① *in vitro* studies

② Determination of the need for *in vivo* studies

③ *in vivo* studies




Variable
Constant
Fc
Murine
–omab
Chimeric
–ximab
Humanised
–zumab
Human
–umab
Antagonism
IgG4
IgG1
Signalling
IgG
CDC
IgG1
IgG2
IgG3
IgM
ADCC
IgG1
IgG3
Vehicle
IgG1
IgG2
IgG4
Ligand
Complement
Prodrugs
Radionuclides
Toxins
Fluorophores
Natalizumab
Daclizumab
Ustekinumab
Infliximab
Muronomab
Rituximab
Alemtuzumab
Rituximab
Alemtuzumab
Rituximab
Not used in MS

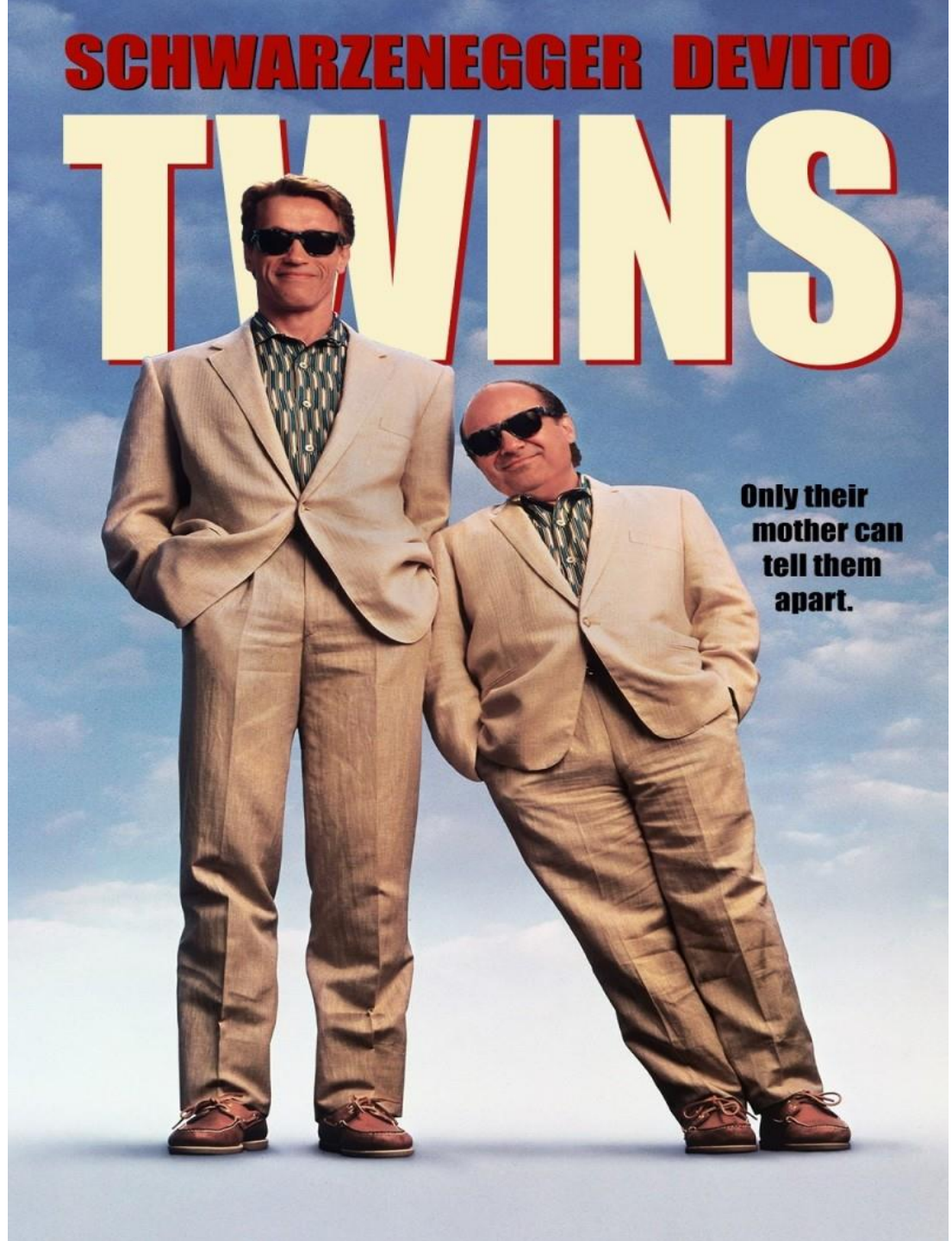



# Step 1: PK/PD
# Step 2: E & S

# E & S

- Adequately powered, randomised, parallel group comparative clinical trial, preferably double-blind, normally equivalence trials.
- Deviation from guidelines should be justified
- Most sensitive patient population and clinical EP preferred
- Comparative S data (immunogenicity)
- Extrapolation of indications: possible based on the overall evidence of comparability




SCHWARZENEGGER DEVITO
TWINS
Only their mother can tell them apart.



# Thank you!




sruiz@aemps.es

## Different Decisions based on Same Data

| Infliximab | EU | Canada | Japan |
|---|---|---|---|
| Rheumatoid arthritis (RA) | √ | √ | √ |
| Ankylosing spondylitis (AS) | √ | √ | |
| Psoriatic arthritis (PsA) | √ | √ | |
| Plaque psoriasis (Ps) | √ | √ | |
| Crohn's disease (Adult and Paediatric CD) | √ | | √ |
| Ulcerative colitis (Adult and Paediatric UC) | √ | | √ |

Dr Jian Wang, Health Canada (EUCRAF 2015)

## Different Decisions based on Same Data

| Bevacizumab | EU | US | Swiss | Canada | Japan |
|---|---|---|---|---|---|
| Lung Cancer | √ | √ | √ | √ | √ |
| Colorectal cancer | √ | √ | √ | √ | √ |
| Breast cancer | √ | Accelerated approval, then withdrawn | √ | Conditional authorization, then withdrawn | √ |
| Glioblastoma | | √ (Accelerated approval) | √ | √ (Conditional authorization) | |
| kidney cancer | √ | √ | | | |
| Ovarian cancer | √ | | | | |

**Approval in 2013**

Dr Jian Wang, Health Canada (EUCRAF 2015)