MHRA
Regulating Medicines and Medical Devices

# The Regulatory and Licensing Process

**Dr Anne Cook, Biologicals Quality Assessor, MHRA**

Medicines and Healthcare Products Regulatory Agency

# Outline of presentation

- Licensing Division at MHRA
- Development/licensing of originator biological medicines
- Basis of regulatory framework for biosimilar medicines
- Importance of analytical/functional data for biosimilars
- Differences and potential clinical impact?
- Non-clinical and clinical requirements
- Approved biosimilar products (to date)

# Licensing Division at MHRA

- Assess applications for marketing authorisations (licenses)
- Assess non-safety variations
- Assess and grant clinical trial authorisations
- Provide scientific/regulatory advice
- Secretariat for Medicines Advisory Bodies (including CHM)
- Approx. 250 staff including pharmacists, scientists, toxicologists, clinicians, statisticians and support staff

# Licensing Division at MHRA

Product Lifecycle Assessment Teams for chemical drugs:

- PLAT 1 Cardiovascular, Diabetes
- PLAT 2 Respiratory, ENT Endocrine, Dermatology
- PLAT 3 CNS, Anaesthetics
- PLAT 4 GI & Nutrition, Blood and Pain
- PLAT 5 Ant-infective, Obstetrics & Gynecology
- PLAT 6 Musculoskeletal, Malignant Disease

**Biologicals & Biotechnology Unit**

Clinical Trials Unit

Statistics Unit

Parallel Import Unit

Expert Committee Support

# What biological products do we licence?

Biological Products:

Products extracted from tissues/blood

Heparins

Polyclonal Antibodies

Plasma-derived FVIII

Allergens extracted from plants

Non-genetically engineered vaccines e.g. some ‘flu vaccines

⇩

**National / DCP / Mutual Recognition procedures**

Biotechnology Products:

*E.coli* / yeast / mammalian cell derived proteins

Advanced Therapy Medicinal Products (ATMP)

Monoclonal antibodies

Recombinant FVIII

Recombinant vaccines

⇩

**Centralised (EU) procedure mandatory**

# Biological medicine product development

| Phase I | Phase II | Phase III |
|---|---|---|
| Pilot scale bioreactor (e.g. 500mL) | Larger bioreactor (e.g. 2,000L) | Commercial scale bioreactor (e.g. 15,000L) |
| Purification | Improved purification | Final purification process |
| Early formulation | Final formulation | Final formulation + presentation |

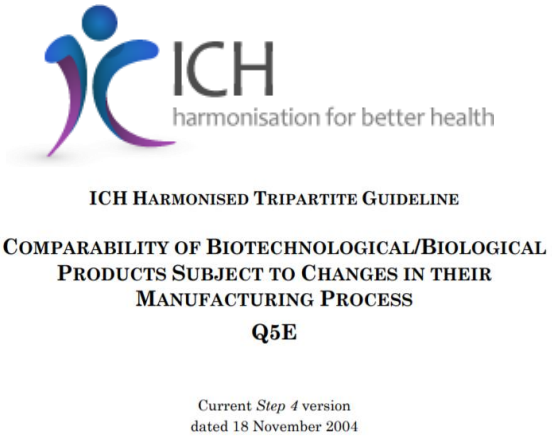
| | | |
|---|---|---|
| Safety/PK/PD | Dose range studies | Pivotal clinical studies |
| Healthy subjects/patients | Safety/efficacy in patients | Safety/efficacy in patients |
| n = 50 - 200* | n = 100 - 400* | n = 1000 - 5000* |

*Numbers indicative only http://www.abpi.org.uk/ourwork/library/guidelines/Documents/guidelines_phase1_clinical_trials.pdf

# Changes in manufacturing process of biological products

- Comparability according to ICH Q5E
  - Comparative data from batches before and after change
  - Extensive characterization for major changes
  - Additional stability studies (also accelerated/stress conditions)

**Process change examples**
New manufacturing site
Changes to fermentation process
Removal/addition of purification steps
Significant changes in raw material
Large change in manufacturing scale



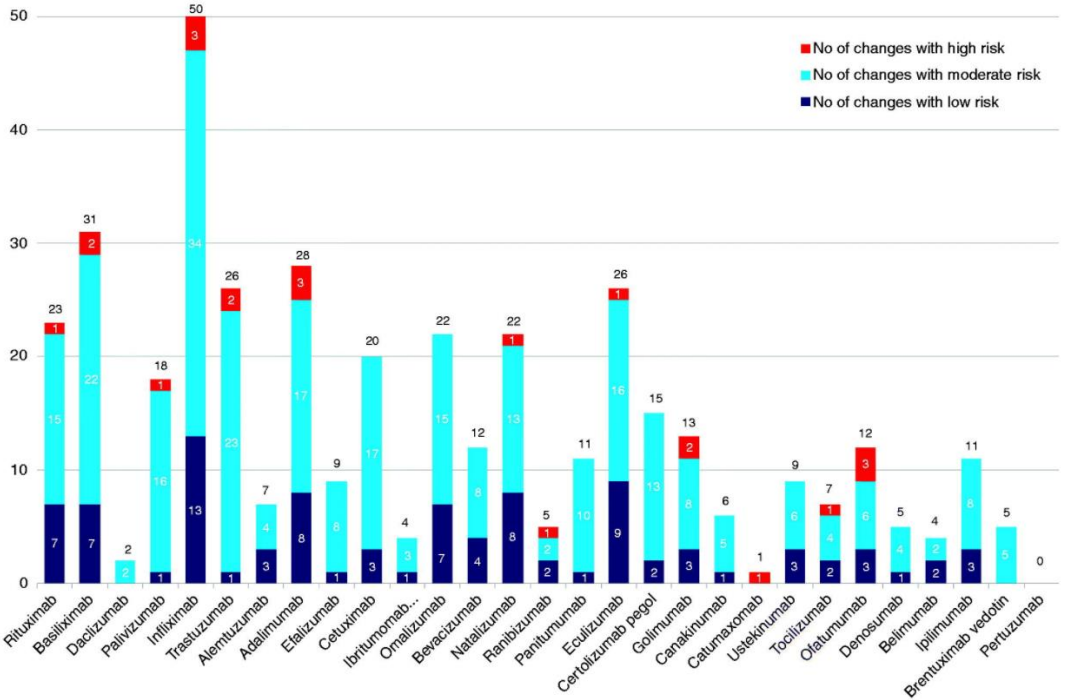
# Changes in manufacturing process of biological products

**Table 5.** Comparability studies needed following changes to the manufacturing process of a medicine produced by biotechnology

| Type of manufacturing change | Expected impact | Comparability studies needed |
|---|---|---|
| 1. Minor change (e.g. adding a more sensitive test method to characterise the active substance) | Does not affect the pharmaceutical quality of the medicine (no impact on product specifications) | Limited physicochemical studies comparing batches before and after the change |
| 2. Significant change (e.g. changes to the cell system used to produce the active substance) | May affect product characteristics or specifications but not expected to affect safety or efficacy | Comprehensive physicochemical and functional in vitro studies |
| 3. Major change (e.g. certain changes in the medicine's formulation) | May possibly affect safety or efficacy | Comprehensive physicochemical and in vitro functional studies complemented as needed by non-clinical and clinical studies |

**Biosimilars in the EU** http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf

# Changes in manufacturing process of biological products

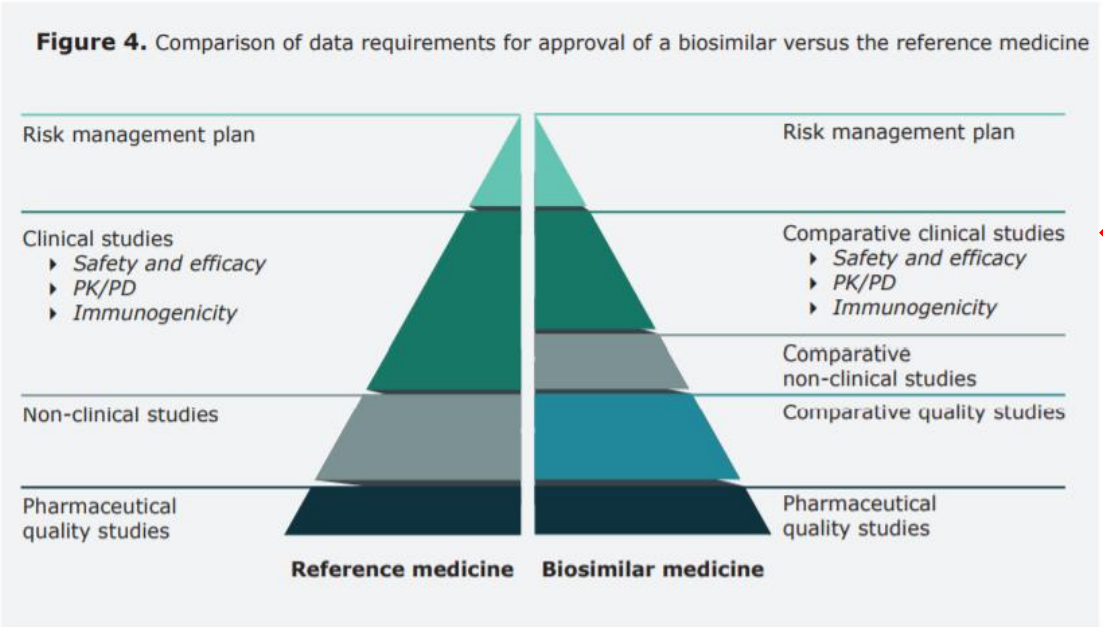



B Vezér et al., Current Medical Research and Opinion (2016): 32(5); 829-834

# The biosimilar concept

- **Full quality dossier (Module 3)**
- **Extensive quality comparability exercise** (physicochemical characteristics, biological activity, *in vitro* functions)
- **Reduced non-clinical and clinical requirements**
  - scientifically appropriate
  - based on previous clinical and regulatory experience of the reference medicinal product
  - flexible (case by case basis)
  - extrapolation of indications
- **Robust post-authorisation pharmacovigilance**

# How is a biosimilar application different from a stand-alone MAA?




To avoid unnecessary repetition of clinical trials

**Biosimilars in the EU** http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf

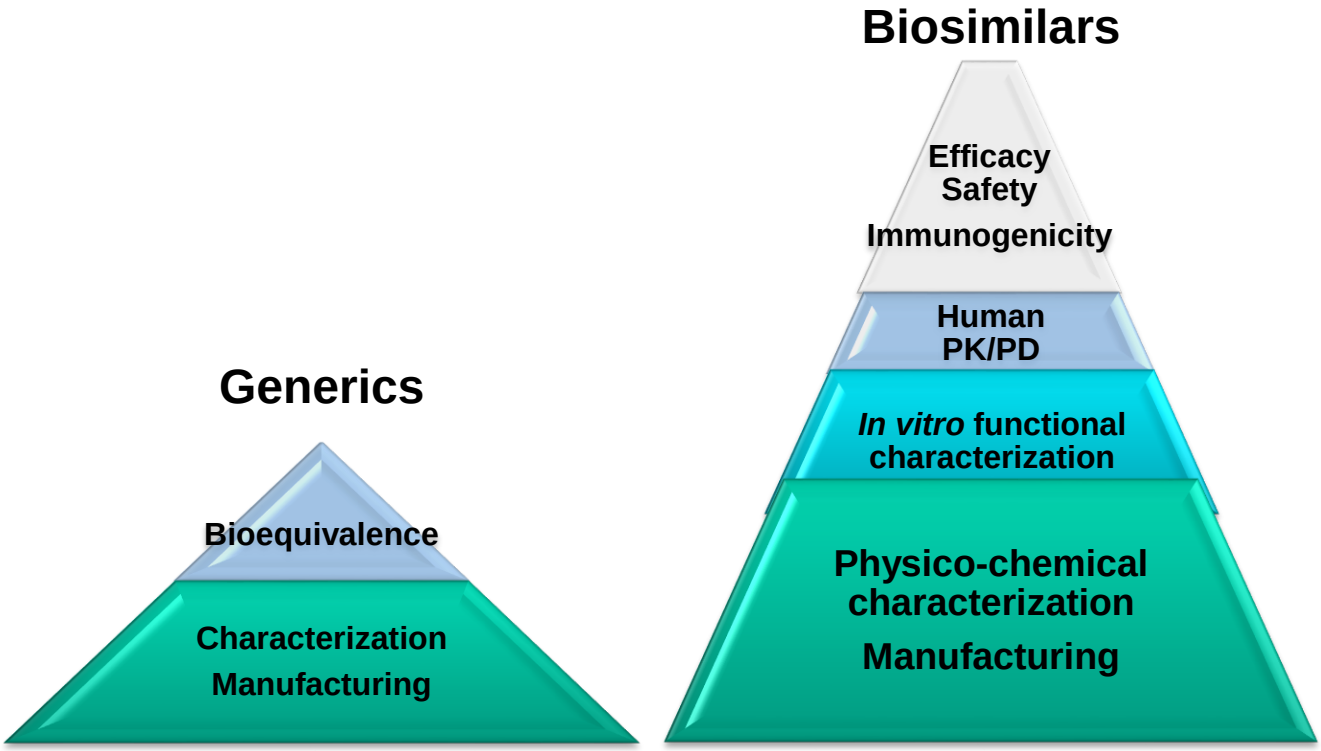
# Biological vs. biosimilar development

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

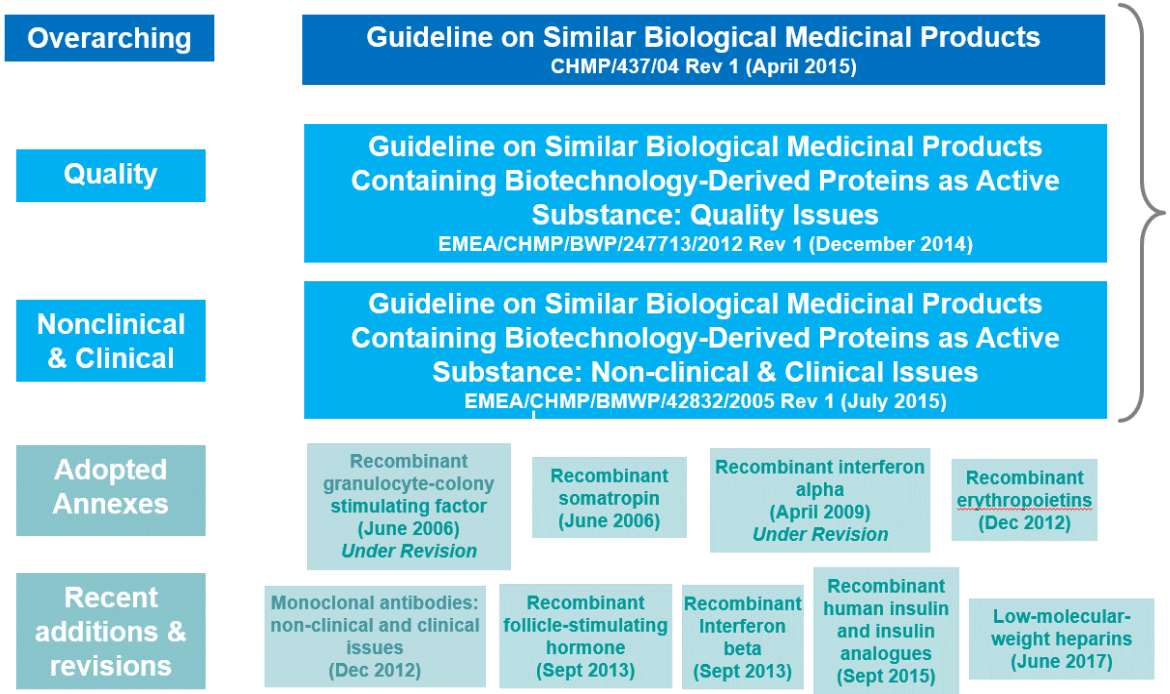
| Biological medicine with new active substance (e.g. reference medicine) | Biosimilar medicine |
|---|---|
| No previous knowledge of safety and efficacy | Builds on knowledge of safety and efficacy from years of clinical use with reference medicine |
| Development aims at demonstrating safety and efficacy 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 |
| Full non-clinical data (pharmacology and toxicology) | Amount of non-clinical data determined by the outcome of quality studies |
| Conventional clinical trials to demonstrate efficacy and safety in all claimed therapeutic indications | Comparative clinical trials to exclude clinically meaningful differences |
| Trials designed mainly to compare with placebo or current standard of therapy using 'hard' endpoints (e.g. long-term outcome, mortality, structural damage) and a relevant patient population to demonstrate benefit | Trials designed mainly to show clinical equivalence with the reference medicine using sensitive endpoints in a population where product-related differences in clinical performance can be detected |
| Positive benefit-risk mainly established on the basis of safety and efficacy studies in the intended population | Positive benefit-risk based on demonstrating biosimilarity (using comparability studies) |

**Biosimilars in the EU** http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf

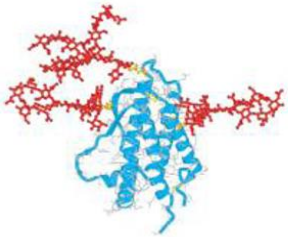
# Generics vs. biosimilars

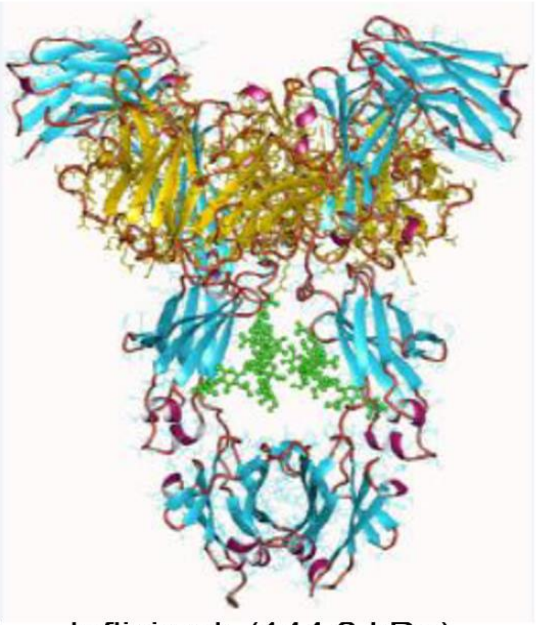


# Guidelines for EU Similar Biological Medicinal Products



# Similar Biological Medicinal Products (biosimilars)





Somatropin (21 kDa)
2006

Epoetin (34 kDa)
2007

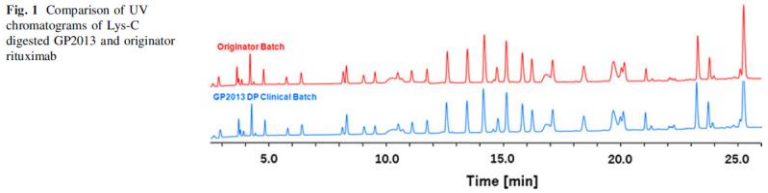
Infliximab (144.2 kDa)
2013

First approval date for certain biosimilars

# Critical quality attributes

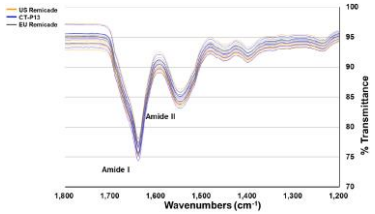
## Structure

- Primary structure identical (except for PTMs e.g. C-terminal lysine)

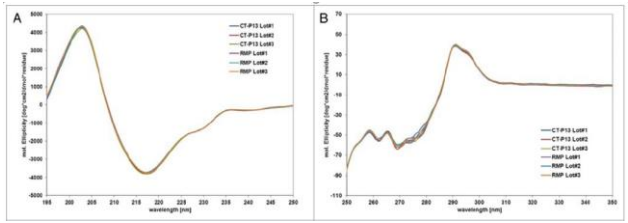



J Visser et al., Biodrugs (2013): 27(5); 495-

- Higher order structure should be comparable




Fourier Transform-IR




Far-UV circular dichroism

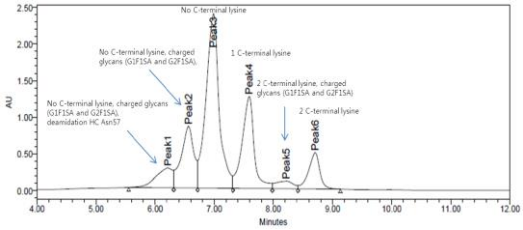
Near-UV circular dichroism

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm484860.pdf
SK Jung et al., mAbs (2014): Vol 6 (5); 1163-1177

- Comparable stability

# Critical quality attributes

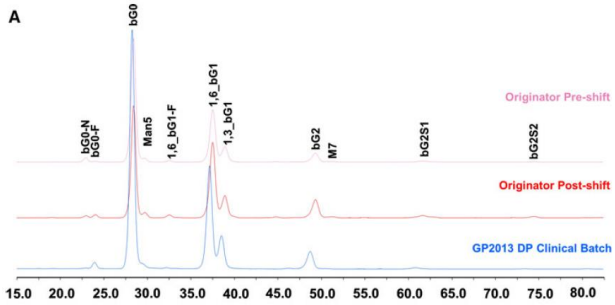
- **Comparable purity/impurities** (monomers, aggregates, fragments, charged isoforms, oxidation, deamidation etc.)




IEC-HPLC peak assignment (Remsima CT-P13)

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm484860.pdf

- **Comparable glycosylation**
  - Microheterogeneity expected (terminal galactose, core fucose, sialic acid)

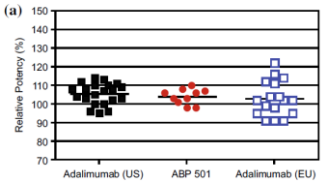


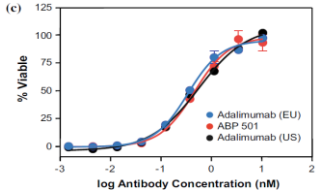

Glycosylation pattern GP2013 and rituximab
J Visser et al., Biodrugs (2013): 27(5); 495-507

# Critical quality attributes

## Biological activity

- Specific binding to target, neutralisation or inhibition of activity

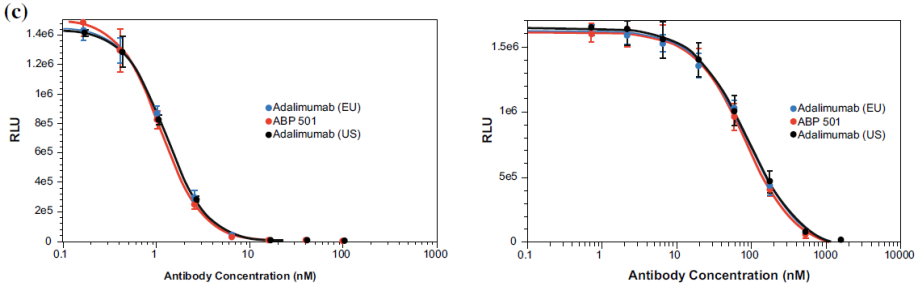



J Velayudhan et al., BioDrugs (2016): 30; 339-351

- Product-specific cell-based assays

For antibodies: Fcγ receptor binding, FcRn binding, C1q binding and CDC, ADCC, apoptosis



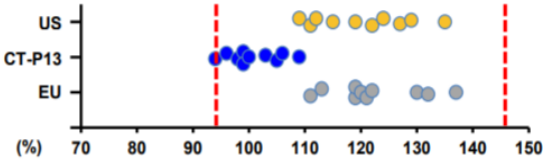

Dose response curves showing FcγRIIIa (158V) binding with (left) and without (right) TNFα

# Critical quality attributes and MoA

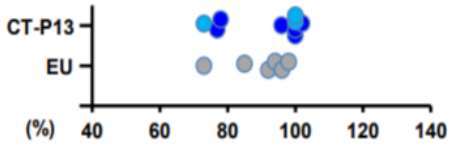
- **Differences identified?**
  - Impact on biological activity (use range of assays)
  - Support arguments with data/orthogonal analysis
  - Consider potential impact on efficacy and safety (MoA)

**Remsima (CT-P13) infliximab vs. Remicade**
www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm484860.pdf

**FcγR111b binding affinity**




**Binding to neutrophils (50% human serum)**

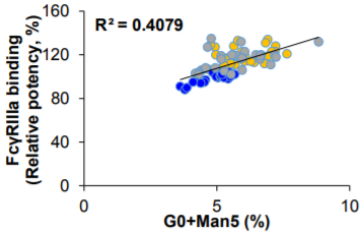



CT-P13 (blue), EU Remicade (yellow), US Remicade (grey)

# Potential clinical impact?

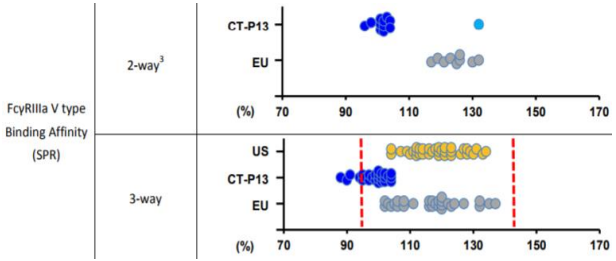
www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm484860.pdf

| Afucosylated glycans | CT-P13 | EU Remicade | US Remicade |
|---|---|---|---|
| G0 | 1.1 ± 0.1% | 2.4 ± 0.4% | 2.2 ± 0.2% |
| Man5 | 4.5 ± 0.3% | 5.0 ± 1.3% | 5.1 ± 0.9% |

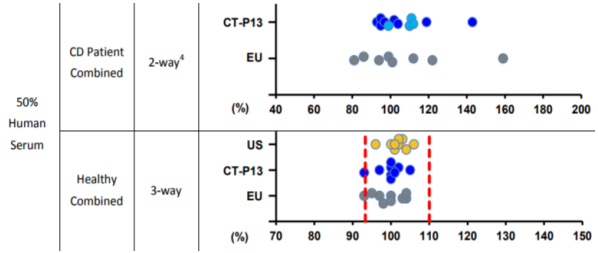



CT-P13 (blue), EU Remicade (yellow), US Remicade (grey)

**FcγR111a receptor binding**



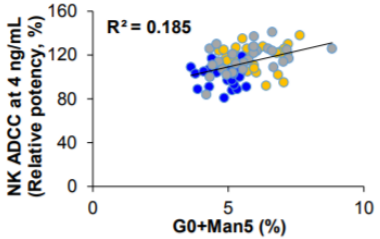

***Ex vivo* binding affinity to NK cells (V/F)**



# Potential clinical impact?

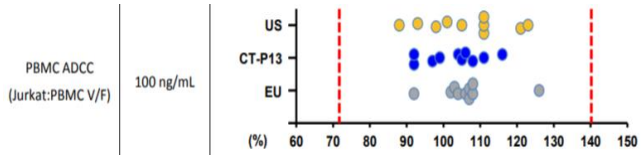
www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm484860.pdf

| Afucosylated glycans | CT-P13 | EU Remicade | US Remicade |
|---|---|---|---|
| G0 | 1.1 ± 0.1% | 2.4 ± 0.4% | 2.2 ± 0.2% |
| Man5 | 4.5 ± 0.3% | 5.0 ± 1.3% | 5.1 ± 0.9% |

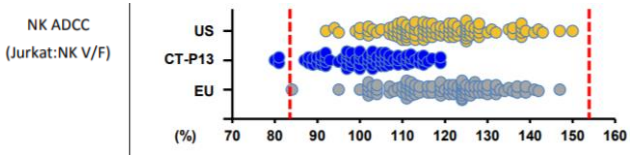



CT-P13 (blue), EU Remicade (yellow), US Remicade (grey)

**ADCC using PBMC cells (Jurkat:PBMC V/F)**



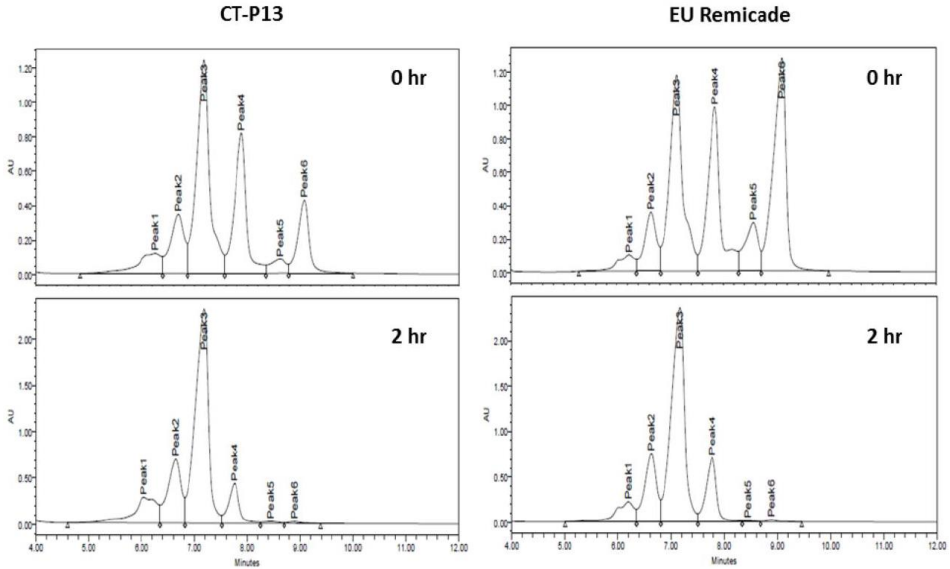

**ADCC using NK cells (Jurkat:NK V/F)**



# Potential clinical impact?

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm484860.pdf

IEC-HPLC profile of CT-P13 and EU Remicade at 1 and 2 hours serum incubation



# Non-clinical requirements

## Risk-based approach

**Always *in vitro* studies**

- comparative
- sensitive assays covering the range of functional activities
- appropriate number of batches

**Usually no need for *in vivo* studies**

- if considered necessary (e.g. potentially relevant quality attributes not detected in the RMP, relevant differences in formulation), focus on PK/PD/safety
- no toxicity study in non-relevant species
- 3Rs principle

# Clinical requirements

## Pre-authorisation

The clinical development is tailored to detect differences

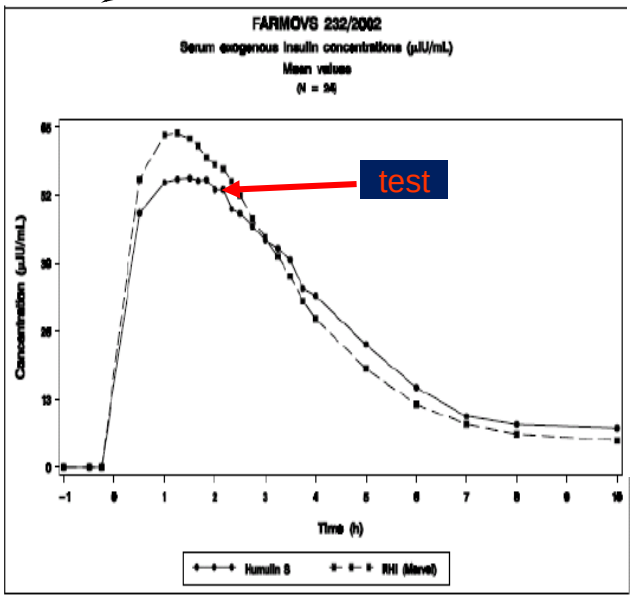
- Comparative PK/PD
  - healthy volunteers and/or patients
  - in some cases, PD may be sufficient as pivotal proof of comparable efficacy (*e.g. absolute neutrophil count for G-CSFs, euglycaemic clamp test for insulins*)
- Comparative efficacy/safety/immunogenicity
  - not to establish patient benefit
  - 'most sensitive model' = able to detect relevant difference

## Post-authorisation

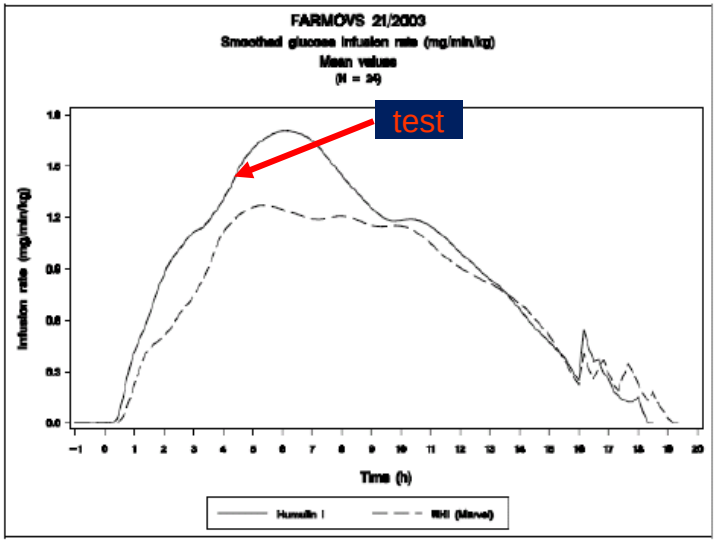
The Risk Management Plan usually includes post-authorisation studies (e.g. continuation of pivotal trial, patient/disease registries)

# PK & PD

PK soluble insulin




http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003858/WC500201969.pdf




PD isophane insulin

http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2013/02/WC500138885.pdf

# PK & PD

**Insulin glargine**

| Studies and dose | | Ratio of LS Geometric Means (90% Confidence Interval for PK; 95% Confidence Interval for PD) | | | | |
|---|---|---|---|---|---|---|
| | | PK Parameters | | | PD Parameters | |
| Study | Dose U/kg | $AUC_{(0\text{-}24)}$ (pmol·hr/L) | $AUC_{(0\text{-}inf)}$ (pmol·hr/L) | $C_{max}$ (pmol/L) | $G_{tot}$ (mg/kg) | $R_{max}$ (mg/kg/min) |
| **Results for Completers** | | | | | | |
| ABEA | 0.5 | 0.91 (0.87, 0.96) | 0.94 (0.88, 1.00) | 0.95 (0.91, 1.00) | 0.95 (0.90, 1.01) | 0.99 (0.93, 1.05) |
| ABEN | 0.5 | 0.97 (0.89, 1.04) | 0.96 (0.87, 1.05) | 0.97 (0.90, 1.04) | 1.02 (0.88, 1.19) | 0.98 (0.87, 1.11) |
| **Results for All Subjects** | | | | | | |
| ABEA | 0.5 | 0.91 (0.87, 0.96) | 0.96 (0.90, 1.02) | 0.95 (0.90, 1.00) | 0.95 (0.90, 1.01) | 0.99 (0.93, 1.05) |
| ABEN | 0.5 | 0.98 (0.91, 1.05) | 0.98 (0.89, 1.07) | 0.99 (0.92, 1.06) | 1.00 (0.87, 1.15) | 0.97 (0.86, 1.09) |

*http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002835/WC500175383.pdf*

# Biosimilars approved in the EU

| | | | | | |
|---|---|---|---|---|---|
| Omnitrope | somatropin | Sandoz | Genotropin | Approval | Apr-06 |
| Valtropin | somatropin | BioPartners | Humatrope | Approval | Apr-06 |
| | | | | Withdrawn | May-12 |
| Abseamed<br>Epoetin alfa Hexal<br>Binocrit | epoetin alfa | Medice<br>Hexal<br>Sandoz | Eprex | Approval | Aug-07 |
| Silapo<br>Retacrit | epoetin zeta | Stada<br>Hospira | Eprex | Approval | Dec-07 |
| Tevagrastim<br>Ratiograstim<br>Biograstim<br>Filgrastim Ratiopharm | filgrastim | Teva<br>Ratiopharm<br>CT Arzneimittel<br>Ratiopharm | Neupogen | Approval<br><br>Withdrawn | Sep-08<br><br>Jul-11 |
| Filgrastim Hexal<br>Zarzio | filgrastim | Hexal<br>Sandoz | Neupogen | Approval | Feb-09 |
| Nivestim | filgrastim | Hospira | Neupogen | Approval | Jun-10 |
| Grastofil<br>Accofil | filgrastim | Apotex<br>Accord Healthcare | Neupogen | Approval | Oct-13<br>Sep-14 |
| Remsima<br>Inflectra | infliximab | Celltrion<br>Hospira | Remicade | Approval | Sep-13 |
| Flixabi | infliximab | Samsung Bioepis | Remicade | Approval | May-16 |
| Benepali | etanercept | Samsung Bioepis | Enbrel | Approval | Jan-16 |
| Ovaleap | follitropin | Teva | Gonal-f | Approval | Sep-13 |
| Bemfola | follitropin | Finox Biotech AG | Gonal-f | Approval | Mar-14 |
| Abasaglar (Abasria) | insulin glargine | Eli Lilly | Lantus | Approval | Sep-14 |

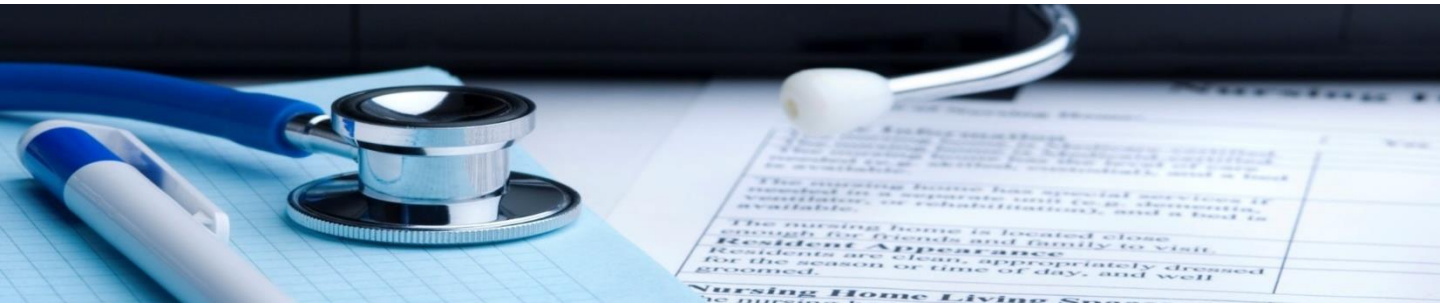
# Approved and ongoing biosimilar applications

| | | | | | |
|---|---|---|---|---|---|
| Truxima | rituximab | Celltrion | MabThera | Approved | Feb-17 |
| Blitzima (duplicate) | rituximab | Celltrion | MabThera | Approved | Jul-17 |
| Ritemvia (duplicate) | rituximab | Celltrion | MabThera | Approved | Jul-17 |
| Rituzena (Tuxella) | rituximab | Celltrion | MabThera | Approved | Jul-17 |
| Rixathon / Riximyo | rituximab | Sandoz | MabThera | Approved | Jun-17 |
| Cyltezo | adalimumab | Boehringer Ingelheim | Humira | Approved | Nov-17 |
| Imraldi | adalimumab | Samsung Bioepis | Humira | Approved | Aug-17 |
| Amgevita/Solymbic | adalimumab | Amgen | Humira | Approved | Mar-17 |
| Ontruzant | trastuzumab | Samsung Bioepis | Herceptin | Positive opinion | |
| Mvasi | bevacizumab | Amgen | Avastin | Positive opinion | |
| Erelzi | etanercept | Sandoz | Enbrel | Approved | Jun-17 |
| Lifmior | etanercept | Pfizer | Enbrel* | Approved | Feb-17 |
| Terrosa | teriparatide | Gedeon Richter | Forsteo | Approved | Jan-17 |
| Movymia | teriparatide | Gedeon Richter | Forsteo | Approved | Jan-17 |
| | pegfilgrastim | | Neulasta | ongoing | CP |
| Lusduna | insulin glargine | Merck Sharp & Dohme | Lantus | Approved | Jan-17 |
| Insulin lispro Sanofi | insulin lispro | Sanofi | Humalog | Approved | Jul-17 |
| Inhixa/Thorinane | enoxaparin | Parmathen | Clexane | Approved | Sep-16 |

= UK Rapporteur or CoRapporteur during evaluation of product

# The Regulatory and Licensing Process for biosimilars

- Robust regulatory approval process for biosimilars
- Quality (manufacturing and controls) same
- Additional comparability exercise (structural and functional) for biosimilars
- Comparable PK (and PD if relevant)
- No clinically meaningful differences (Q, S & E)
- **Clinically equivalent**
- Recommend prescribing by brand name (traceability)



# © Crown copyright 2017