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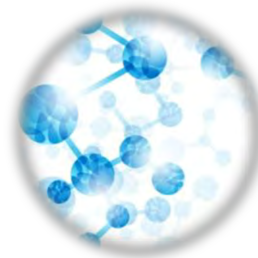
GaBI Educational Workshops

14 June 2016, Hilton Bogotá, Colombia

First INVIMA Educational Workshop on Assessment of SIMILAR BIOTHERAPEUTIC PRODUCTS



Principles and challenges related to manufacturing process development and demonstration of analytical comparability for biosimilars – the infliximab case as an example

Niklas Ekman, PhD

14 June 2016

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Principles and challenges related to manufacturing process development and demonstration of analytical comparability for biosimilars – the infliximab case as an example

GaBI/ INVIMA educational workshop on assessment of similar biotherapeutic products

14 June 2016, Bogota, Colombia

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Agenda

1. EU Biosimilars - The concept of analytical similarity
2. Manufacturing process development
3. The pivotal evidence for analytical biosimilarity
4. Product experience – reflections from assessment of a marketing authorisation application

www.theplanetfunniestanimals.com

Disclaimer: The views expressed are those of the presenter and should not be understood or quoted as being made on behalf of the European Medicines Agency or its scientific Committees

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What makes biotech products special

- Biotech products are large and complex molecules
- The use of living cells for production will always introduce heterogeneity into the drug substance
- Variability is inherent in biologics, no batch of any biologics is fully identical to another batch
- The link between a specific quality attribute and the clinical outcome can be difficult to determine
- “The product is the process” has been postulated - what about real life experience?

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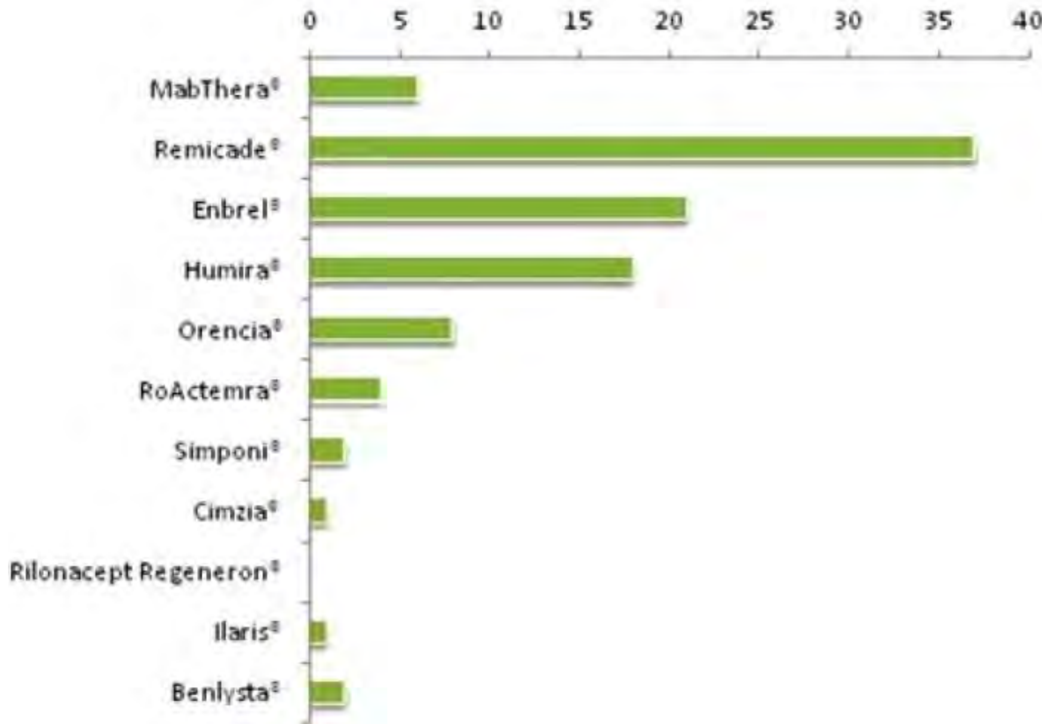
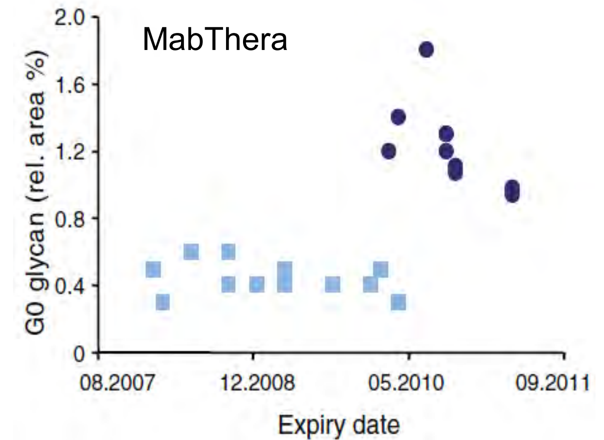
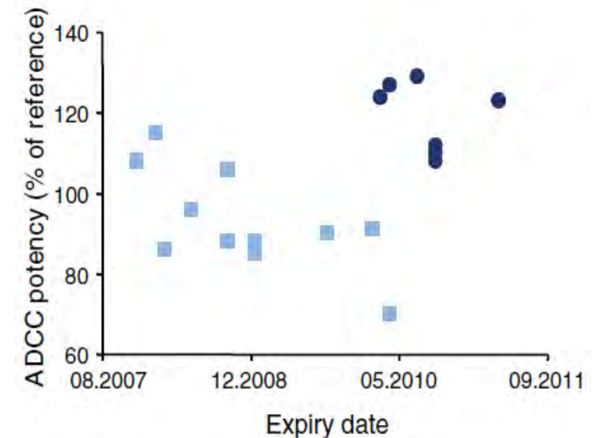
Manufacturing process changes are common for all biologics



Schneider C., Ann Rheum Dis March 2013 Vol 72 No 3





Schiestl M. et al, Nat Biotech, April 2011

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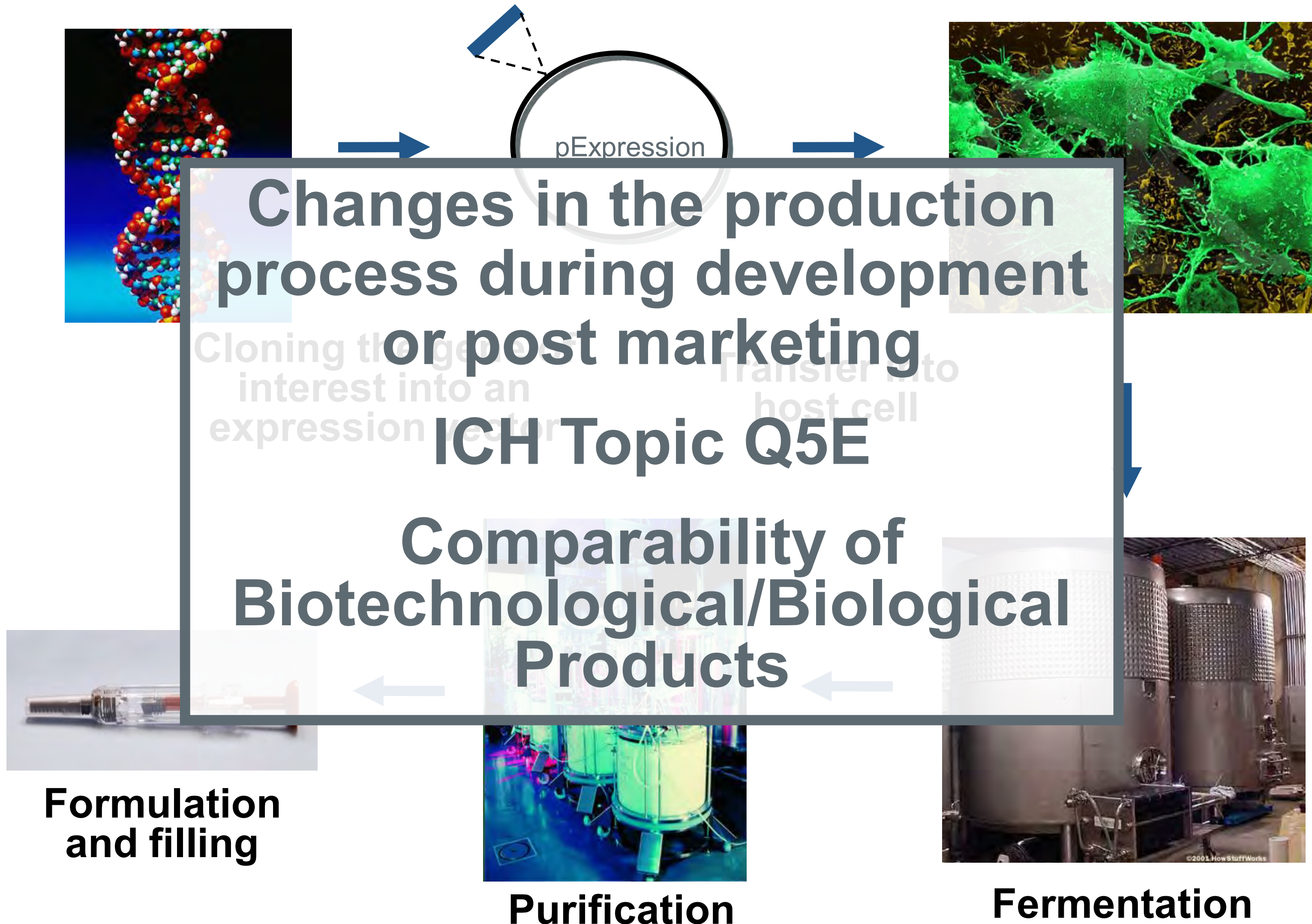

Changes in the production process during development or post marketing

ICH Topic Q5E

Comparability of Biotechnological/Biological Products

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ICH Topic Q 5 E
Comparability of Biotechnological/Biological Products

"..where the relationship between specific quality attributes and safety and efficacy has not been established, and *differences between quality attributes of the pre- and post-change product are observed, it might be appropriate to include a combination of quality, nonclinical, and/or clinical studies in the comparability exercise*."

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf

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What is a biosimilar?

Current EU regulatory definition of biosimilars

A biosimilar is a biological medicinal product that *contains a version of the active substance* of an already authorised 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*

- ✓ *The scientific principles of a biosimilar comparability exercise are based on those applied for evaluation of the impact on changes in the manufacturing process of a biological medicinal product*

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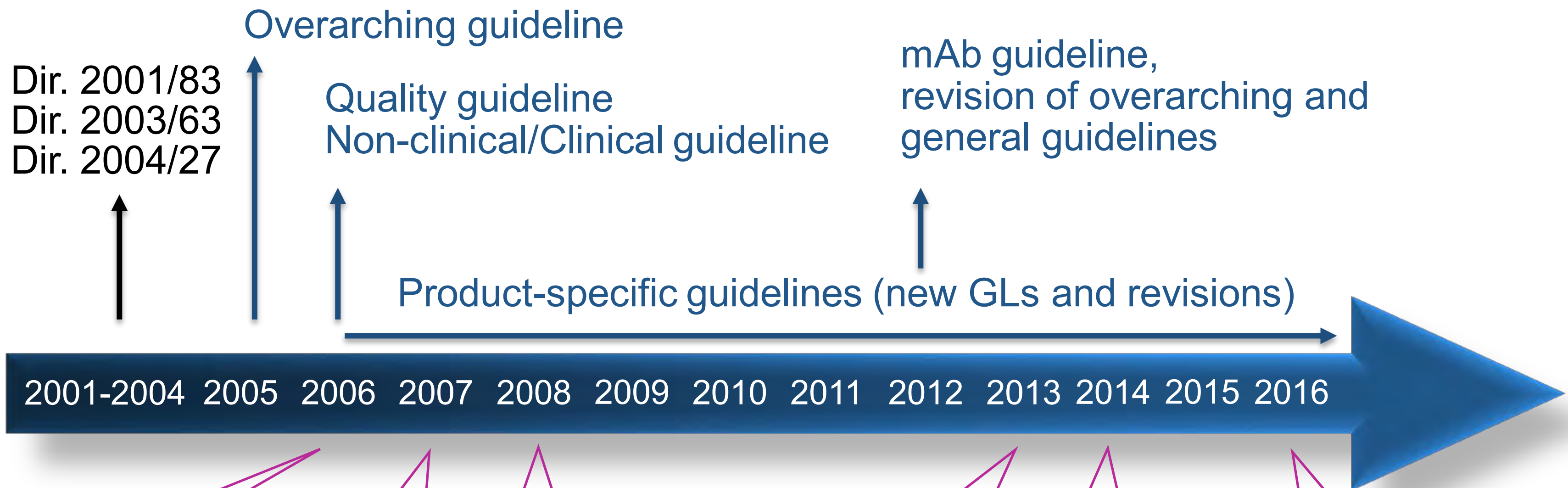
Evolution of Biosimilars in the EU



First biosimilar somatropin

First biosimilar eopoetin

First biosimilar filgrastim

First biosimilar mAb and follitropin alfa

First biosimilar insulin glargine

First biosimilar etanercept

Product authorisation

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Assessment experience in the EU

- 31 Marketing authorisation applications for biosimilars reviewed by the CHMP
  - 22 positive, 7 withdrawn during evaluation, 2 negative
- 20 biosimilar medicinal products (13 active substances) currently holding a valid marketing authorisation
  - 1 somatropin, 5 epoetin (two AS), 8 filgrastim (5 AS), 3 infliximab (two AS), 2 follitropin alfa (two AS), 1 insulin glargine
  - 2 authorisations withdrawn by the MA holder post-approval
- 12 biosimilar MA applications under review (May 2016)
  - Adalimumab (2), enoxaparin sodium (2), etanercept (1), insulin glargine (1), pegfilgrastim (3), rituximab (1), teriparatide (2)
- Over 200 scientific advice procedures completed in 2006-2015
  - Majority on mAbs; ~80% in 2015

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General principles for biosimilar development

- In principle, the concept of a biosimilar is applicable to any biological medicinal product
- The success of developing a biosimilar depends on;
  - The ability to *manufacture a close copy version* of the reference medicinal product in a consistent manner
  - The ability to *perform thorough physicochemical and biological characterization* and to *understand the clinical relevance* of any differences detected
  - The ability to demonstrate *bioequivalence*
  - The availability of *suitable clinical models*; sensitive endpoints, possibility to identify relevant comparability margins

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Biosimilar vs Reference Medicinal Product - How close is close enough?

- Must be the same
  - The amino acid sequence
  - Posology and the route of administration
- Must be similar
  - The active substance in terms of molecular and biological characteristics
- Need to be justified
  - Differences in strength, pharmaceutical form, formulation, excipients or presentation
- Not allowed
  - Intended changes to improve efficacy (”biobetters”)

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1. EU Biosimilars - The concept of analytical similarity
2. **Manufacturing process development**
3. The pivotal evidence for analytical biosimilarity
4. Product experience – reflections from a recent marketing authorisation application

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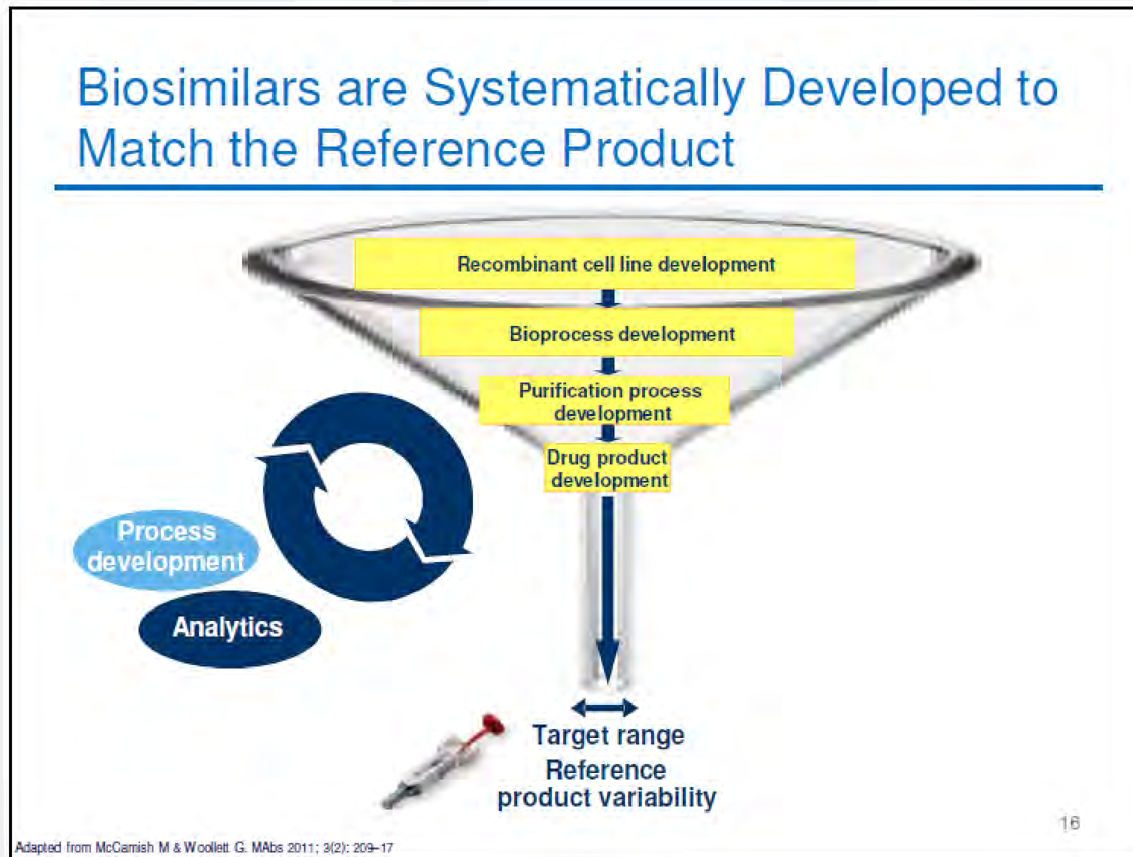
Biosimilar manufacturing process development



- Variability is inherent to biologics
- For each (critical) quality attribute, the variability is controlled within an acceptable range
- Attribute variability as measured from the reference product, forms the basis for biosimilar development

Slide presented by Sandoz at Oncologic Drugs Advisory Committee meeting on Zarxio (filgrastim), January 7, 2015

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Manufacturing process development - Quality Target Product Profile (QTPP)

- A prospective summary of the quality characteristics of a drug product that ideally will be achieved
- Based on data collected on the reference medicinal product; publicly available information and data obtained from extensive characterisation
- The importance of the quality attributes/ characteristics for the biological function of the protein need to be understood
  - Single or multiple mode of action?
  - Impact of post-translational modifications?
- Detailed at an early stage of development and forms the basis for the development of the biosimilar product and its manufacturing process

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Reverse Engineering Approach

- Expression system development
  - Needs to be carefully considered taking into account expression system differences that may result in undesired consequences; atypical glycosylation, higher variability or a different impurity profile
- Upstream process development
  - To match product attributes; Media composition, fermentation parameters, growth characteristics etc.
- Downstream process development
  - To match product variants; Purification principles and chromatographic parameters used

The goal is to design a manufacturing process that consistently produces a high quality biosimilar product fulfilling the established Quality Target Product Profile

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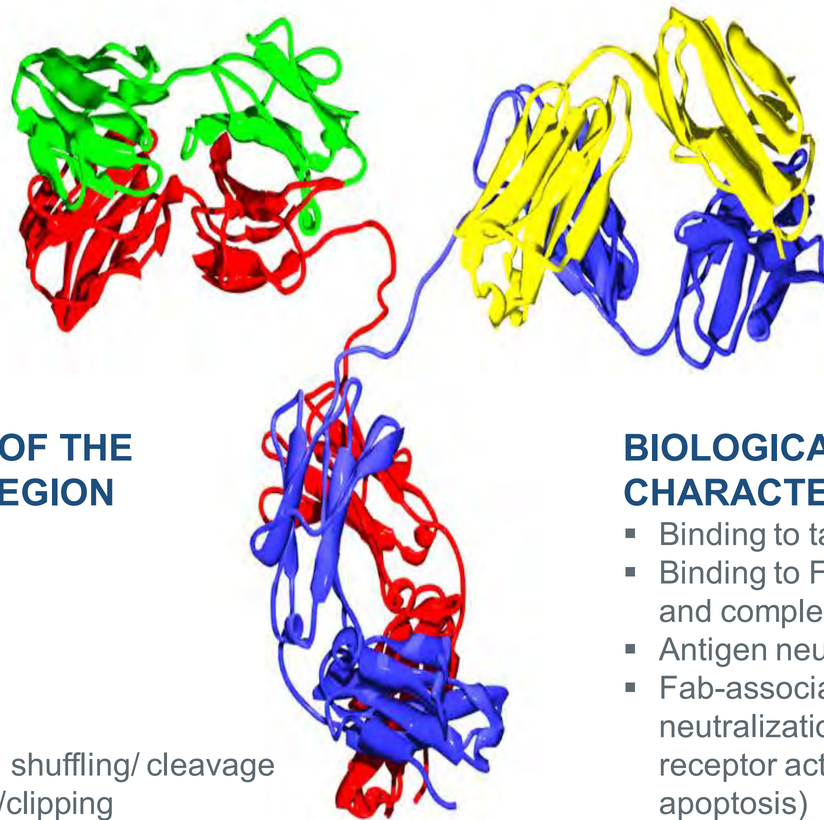
Analytical and functional characterisation of a typical monoclonal antibody

ATTRIBUTES OF THE VARIABLE REGION

- Deamidation
- Oxidation
- N-term Pyro-Glu
- Glycosylation
- Glycation
- Conformation changes



PHYSICOCHEMICAL CHARACTERITICS

- Structure (primary, higher order structures)
- Molecular mass
- Purity/ impurity profiles
- Charge profile
- Hydrophobicity
- O- and N-glycans

ATTRIBUTES OF THE CONSTANT REGION

- Deamidation
- Oxidation
- Acetylation
- Glycation
- Glycosylation
- C-term Lys
- Di-sulfide bond shuffling/ cleavage
- Fragmentation/clipping
- Conformation changes

BIOLOGICAL/ FUNCTIONAL CHARACTERISTICS

- Binding to target antigen(s)
- Binding to Fc γ receptors, FcRn and complement
- Antigen neutralisation (if relevant)
- Fab-associated functions (e.g. neutralization of a soluble ligand, receptor activation, induction of apoptosis)
- Fc-associated functions (ADCC and CDC)

Figure from Wikipedia

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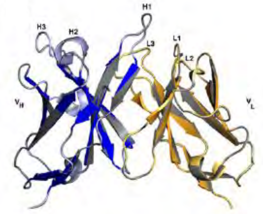
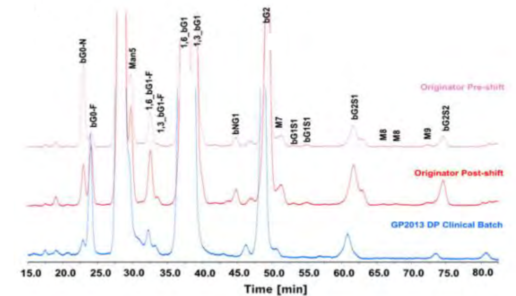
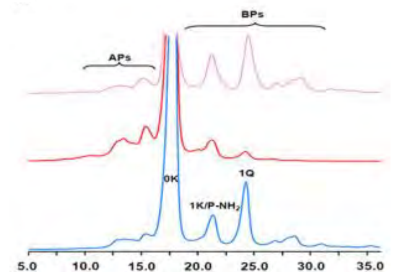
Analytical tools commonly used for mAb characterisation



- Amino acid sequence and modifications
  - MS, LC-MS, peptide mapping, N- and C-terminal sequencing, AA content
- Disulphide bridging, protein folding and higher-order structures
  - Peptide mapping, Ellman's assay, CD, FTIR, HDX-MS, NMR, DSC, X-ray crystallography
- Glycosylation and glycation
  - Anion exchange, enzymatic digestion, peptide mapping, CE, MS, BAC
- Size heterogeneity
  - SEC, AUC, AF4, MALDI-TOF, CD-SDS, SDS-PAGE
- Heterogeneity of charge and hydrophobicity
  - IEF, cIEF, IEX, RP-HPLC
- Functional characterisation and bioassays
  - Target and/or receptor binding; SPR, ELISA, cell-based assays
  - Bioassays; Signal transduction, ADCC, CDC, other cell-based assays





Figures from Visser J. et al. BioDrugs. 2013 Oct;27(5):495-507

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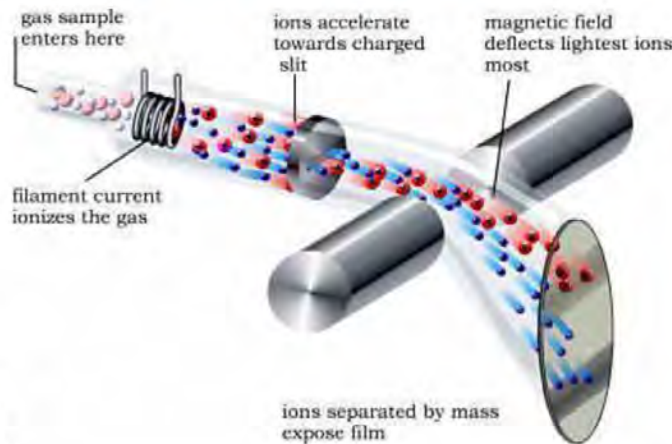
Rapid advances in analytical sciences

The Sensitivity of Mass Spectrometer (MS) Methods is Progressing Rapidly

Year	Detection limit of peptide (pmol)
1990	100
1993	10
1997	1
2000	0.1
2003	0.01
2005	0.001
2008	0.0001
2011	0.00001



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AMGEN

- 10 000 fold increase in sensitivity in 10 years
- 10 million fold increase in sensitivity in 20 years!

Slide presented by Tony Mire-Sluis (Amgen) at CASSS Mass Spec 2012

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1. EU Biosimilars - The concept of analytical similarity
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The ”pivotal” evidence for analytical similarity

- An extensive, side-by-side (whenever feasible) comparability exercise is required to demonstrate high similarity
  - Composition, physical properties, primary and higher order structures, purity, product-related isoforms and impurities, and biological activity
  - Orthogonal methods should be used whenever possible
  - The aim is to show high similarity on the drug product level using material produced with the final (commercial) manufacturing process using sensitive analytical methods
- Quantitative comparability ranges should be established
  - Ranges should be based primarily on the measured quality attribute ranges of reference product and should not be wider than the range of variability of the representative reference product batches

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The ”pivotal” evidence for analytical similarity

- Any differences detected in quality attributes must be justified in relation to safety and efficacy
  - It may be challenging to claim biosimilarity if relevant quality differences are confirmed, clinical data cannot be used to justify substantial differences in quality attributes
  - For justifying differences in low criticality attributes, previous knowledge might be sufficient
  - For medium to high criticality attributes, Structure Activity Relationship (SAR) studies are usually required
- Additional comparative stability studies under accelerated conditions can be useful to compare degradation pathways, i.e. to reveal “hidden” differences

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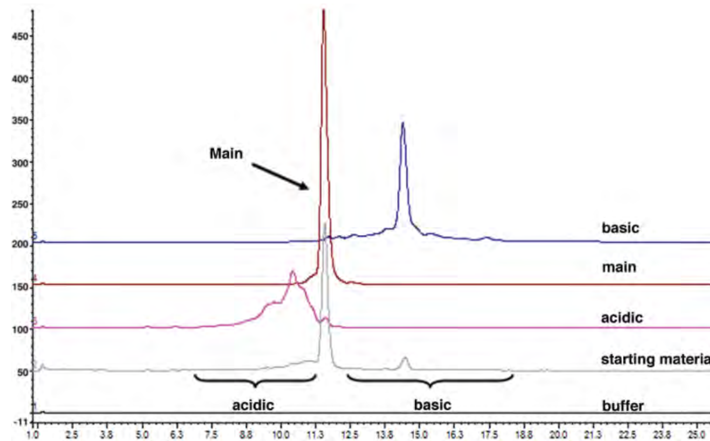
Example of a SAR study – The biological impact of IgG1 charge variants

Khawli L. et al mAbs 2:6, 613-624; November/December 2010

1. Separation and isolation of IEC fractions

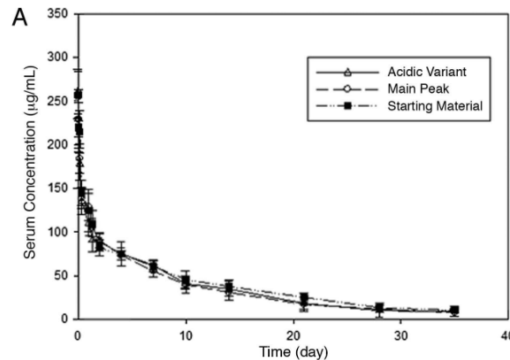


2. Identification of variants present in isolated fractions

Table 3. Analytical characterization of isolated charge variant fractions

Method	Percentage of variants detected[a]
Acidic Variant Fraction	
IEC +/- Sialidase treatment	29% Sialylated
Reduced CE-SDS	7% Incompletely reduced
Non-reduced CE-SDS	29% Reduced disulfide
Boronate chromatography	17% Glycated
Peptide Map with Mass Spectrometry	18% Deamidated[b]
Basic Variant Fraction	
Peptide Map with Mass Spectrometry (for identification) and IEC (for quantification)	85% C-terminal heavy chain variants 15% N-terminal Val-His-Ser light chain variants

3. Rat PK study on isolated fractions



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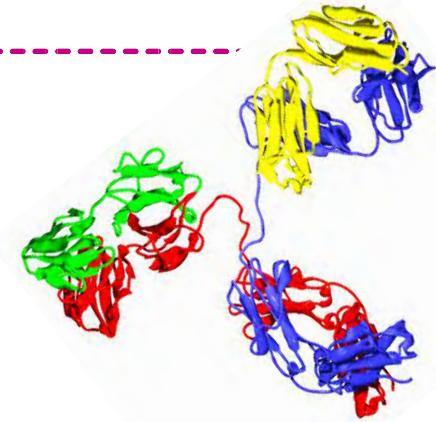

Assessment experience from addressing the impact of glycosylation differences observed for a biosimilar monoclonal antibody

Marketing Authorisation Application for Remsima/ Inflectra[1]

[1] European public assessment report (EPAR) available at www.ema.europa.eu

Analytical Methods in Structural and Physicochemical Biosimilarity Studies

Primary Structure
- Peptide Mapping (HPLC)
- Peptide Mapping (LC-MS)
  - Deamidation – HC Asn57, HC Asn318, HC Asn364, HC Asn387, LC Asn41
  - Oxidation – HC Met255
  - C-terminal variant – HC Lys450
- Intact Mass (LC-MS)
  - Light chain
  - Heavy chain K0 – G0, G0F, G1F, G2F
  - Heavy chain K1 – G0F, G1F, G2F
- Amino Acid Analysis/Molar Absorptivity
  - Aspartic acid, Glutamic acid, Serine, Histidine, Glycine, Threonine, Arginine, Alanine, Tyrosine, Valine, Methionine, Phenylalanine, Isoleucine, Leucine, Lysine, Proline, Molar Absorptivity, Extinction Coefficient
- N-terminal Sequencing
  - Heavy chain
  - Light chain
- C-terminal Sequencing
  - Heavy chain
  - Light chain

Higher Order Structure
- FTIR
  - Amide I
  - Amide II
  - A
  - B
  - C
- DSC
  - Transition 1
  - Transition 2
  - Transition 3
- CD
- Free Thiol Analysis
- Disulfide Bond
  - H3-H12: 22-98
  - H15-H16: 147-203
  - H20-L19: 223-214
  - H21-H21: 229-229/232-232
  - H23-H29: 264-324
  - H37-H42: 370-428
  - L2-L7: 23-88
  - L10-L17: 134-194
- Antibody Array

Content
- Protein Concentration (UV_{280})

Glycosylation
- HPAEC-PAD
  - G0F, Man5, G0, G1F, G2F, SA1, SA2
- NP-UPLC
  - G0F-GN, G0, G0F, MAN5, G1F-GN, G1, G1F, G1F', G2, G2F, G1-GN+NGNA, G1F-GN+NGNA, G1F+NGNA, G1F'+NGNA, G2+NGNA, G2F+NGNA, G2F+2NGNA, Unknown species
- N-linked Glycan Analysis
  - Man5, G0F-GlcNAc. G0, G0F, G1F, G2F, G1F1NeuGc, G2F1NeuGc
- Sialic Acid Analysis
- Monosaccharide Analysis
  - Fuc, GlcNAc, Gal, Man
- Glycation (LC-ES-MS)
  - Light chain
  - Heavy chain

Purity/Impurity
- SEC-HPLC
  - Monomer
  - Dimer
- SEC-MALS
  - Monomer
  - Dimer
  - Monomer (MW)
  - Dimer (MW)
- AUC
  - Monomer
  - Higher species
- Non-reduced/Reduced CE-SDS
  - Intact IgG (NR)
  - H+L (R)
  - Non-glycosylated HC (R)
- Sub-visible particles (MFI & HIAC)

Charge Variants
- IEF
- IEC-HPLC
  - Peak 1, Peak 2, Peak 3, Peak 4, Peak 5, Peak 6

Excipients
- pH
- Polysorbate 80
- Sucrose

Slide presented at FDA Arthritis Advisory Committee Meeting for CT-P13 Feb 09, 2016;
http://www.fda.gov/AdvisoryCommittees/Calendar/ucm481969.htm

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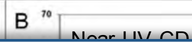
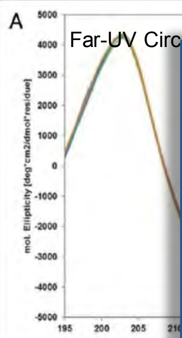
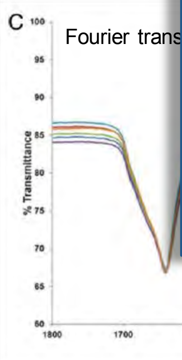
Primary structure; LC-MS peptide mapping

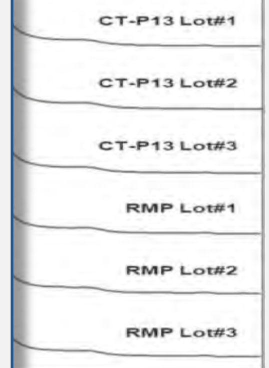


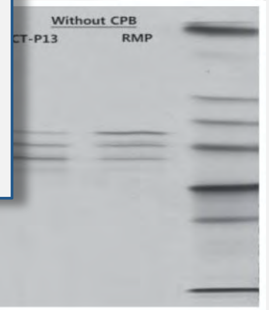
Higher order structures



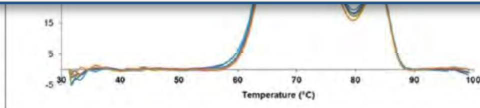


Purity/impurity profile





Biological activity; binding and neutralisation of sTNFα



Pictures from Jung et al., mAb 6:5, 1163-1177, 2014 and FDA Arthritis Advisory Committee Meeting for CT-P13, Feb 09, 2016; http://www.fda.gov/AdvisoryCommittees/Calendar/ucm481969.htm

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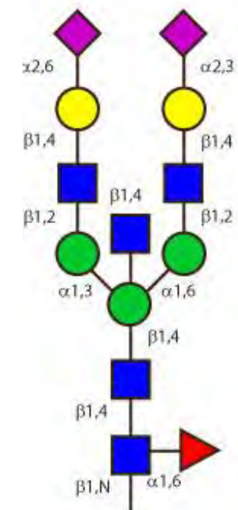
Summary of analytical similarity assessment

- High similarity between the biosimilar and the reference demonstrated for
  - Primary, secondary and tertiary structures
  - *In vitro* TNFα neutralisation, binding affinity (soluble and transmembrane TNFα, TNFβ, FcγRIa, FcγRIIa, FcRn, C1q), in vitro functional tests (apoptosis, CDC, ADCC using PBMNC effector cells from healthy volunteers)
- Minor differences reported for
  - C-terminal lysine content, aggregates, intact IgG level, charged molecular variants, glycosylation pattern
  - Binding to FcγRIIIa

Glycosylation and effector function analyses

- Recombinant mAbs contain a large amount of different glycan types
- As some of the glycan structures may affect activity, clearance and/or immunogenicity, detailed comparison of glycan structures is usually necessary
  - N-linked glycan analysis; site, structure and occupancy
  - Carbohydrate content; neutral and amino sugars
  - Sialic acid content (NANA and NGNA)
  - Antennary profile, high-mannose variants
- Binding to Fc receptors (FcγRI, FcγRII and FcγRIII) and complement (C1q)
- Fc associated functional studies; ADCC and CDC
  - Especially if the MoA is known to involve Fc functions



Tabular overview of clinical studies

Protocol	Design	Objectives	Treatment	Study population
CT-P13 1.2 (pilot study)	Prospective Phase 1, randomised double-blind, parallel-group, multiple single-dose intravenous (i.v.) infusion, multicentre	Primary: To determine C_{max}, PK profiles of CT-P13 and Remicade at Weeks 0, 2 and 6 Secondary: PK profile, PD, efficacy, and safety of CT-P13 in comparison to Remicade up to Week 102.	CT-P13 plus MTX or Remicade plus MTX	RA patients with active disease while receiving MTX Planned: 20 Randomised: 19 CT-P13: 9 Remicade: 10
CT-P13 1.1 PK equivalence (Study name: PLANET AS)	Prospective Phase 1, randomised, double-blind, multicentre, multiple single-dose i.v. infusion, parallel-group	Primary: To demonstrate comparable PK at steady state in terms AUC_τ, $C_{max,ss}$ between CT-P13 and Remicade determined between Weeks 22 and 30. Secondary: long-term efficacy, PK and overall safety up to Week 54	CT-P13 or Remicade	AS patients with active disease Planned: 246 (ratio: 1:1) Randomised: 250 CT-P13: 125 Remicade: 125
CT-P13 3.1 Therapeutic equivalence (Study name: PLANET RA)	Prospective Phase 3, randomised, double-blind, multicentre, multiple single-dose i.v. infusion, parallel-group	Primary: To demonstrate that CT-P13 is equivalent to Remicade, in terms of efficacy as determined by clinical response according to ACR20 at Week 30. Secondary: long-term efficacy, PK, PD, and overall safety up to Week 54	CT-P13 plus MTX or Remicade plus MTX	RA patients with active disease while receiving MTX Planned: 584 (ratio: 1:1) Randomised: 606 CT-P13: 302 Remicade: 304

ACR20=20% improvement according to the ACR criteria; AS=Ankylosing spondylitis; AUC_τ=Area under the concentration-time curve over the dosing interval; Cmax=maximum serum concentration; i.v.=intravenous; MTX=methotrexate; PK=Pharmacokinetics; PD=Pharmacodynamics; RA=Rheumatoid arthritis

From Remsima EPAR available at www.ema.europa.eu

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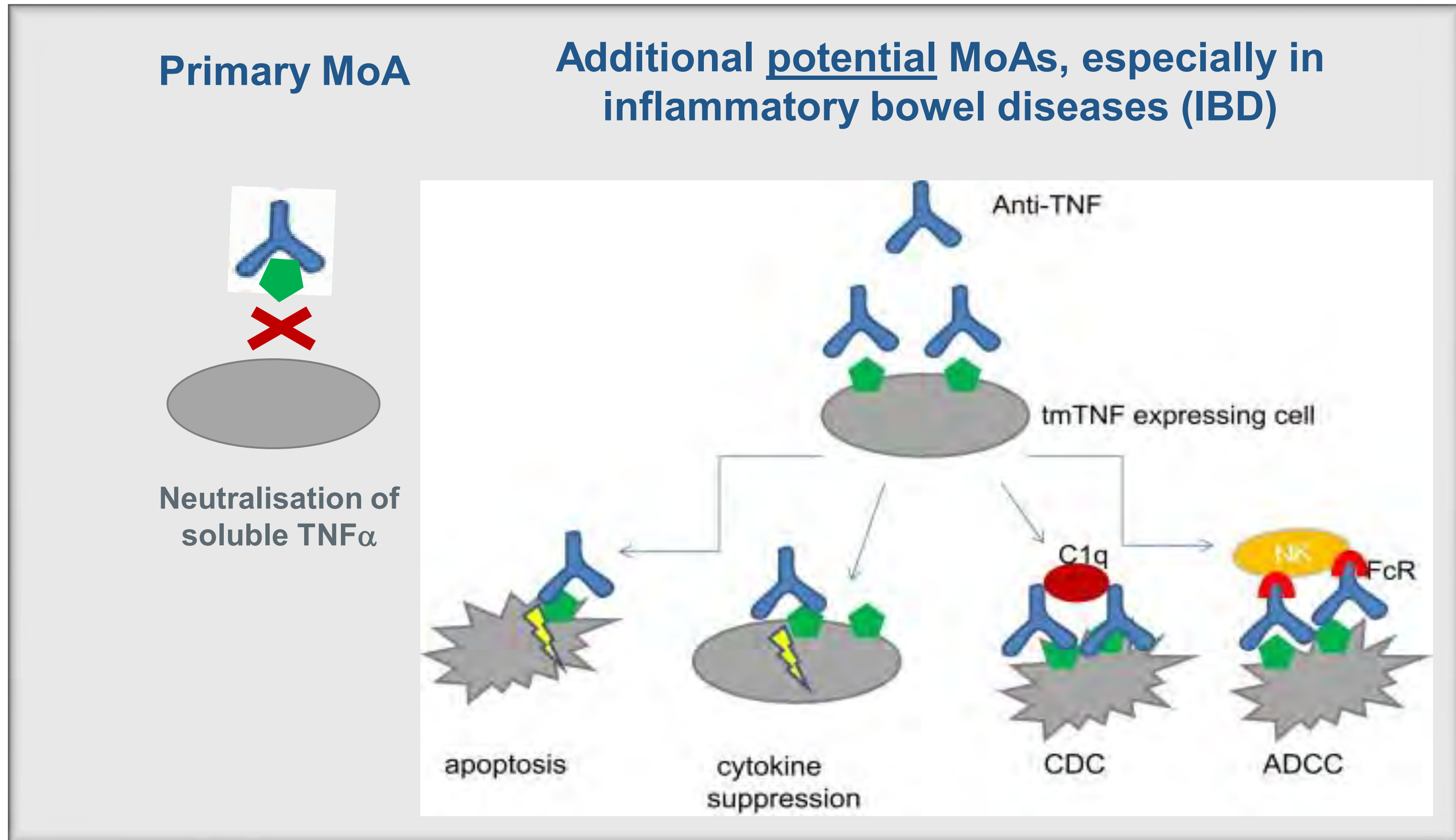
Potential mechanisms of action for anti-TNFs



Modified from Thalayasingam N. et al., Best Pract Res Clin Rheumatol. 2011 Aug;25(4):549-67

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Can efficacy and safety data be extrapolated to all Remsima/Inflectra indications applied for?

- Remsima was shown to contain a lower level of afucosylated glycans than Remicade, resulting in a lower binding affinity to FcγRIIIa and FcγRIIIb
- Directive 2001/83, part II, Annex 1

  In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications

➢ As Fc-mediated functions could potentially be involved in the mode of action of infliximab, the Company was asked to provide further experimental data, in combination with an overall discussion, confirming that the differences detected do not affect efficacy or safety in any of the applied indications

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Test Method	Key Findings
	F(ab')2 related
Comparative apoptosis of Remsima and Remicade	The apoptotic effects by reverse signalling through tmhTNFα for Remsima and Remicade were comparable. No statistically significant differences were detected at any time point.
Comparative Reverse signalling	Blockade of pro-inflammatory cytokine production by reverse signalling through tmhTNFα for Remsima and Remicade were comparable, using PBMC from either healthy donors or CD patients.
Effect of blocking soluble TNFα in *in vitro* IBD model: Suppression of cytokine secretion in epithelial cell line by blocking soluble TNFα	Suppression of pro-inflammatory cytokine (IL-6 and IL-8) secretion from co-stimulated epithelial cell line was shown to be comparable and dose dependent for Remsima and Remicade; no statistical difference in pro-inflammatory cytokines suppression was found.
Effect of blocking soluble TNFα in *in vitro* IBD model: Suppression of apoptosis in epithelial cell line cells by blocking soluble TNFα	Suppression of epithelial cell line apoptosis was shown to be comparable for Remsima and Remicade.
	Fc-F(ab')2 related
Comparative complement-dependent cytotoxicity (CDC) of Remsima and Remicade	CDC effects of Remsima and Remicade against tmhTNFα-Jurkat cells by lysis were comparable. No statistically significant differences were detected in relative CDC activity.
Comparative antibody-dependent cell-mediated cytotoxicity (ADCC) of Remsima and Remicade using tmhTNFα-Jurkat cells as target cells and human PBMC as effector cells	Remsima and Remicade had comparable ADCC activity and no statistically significant differences were detected.
Comparative ADCC of Remsima and Remicade using tmhTNFα-Jurkat cells as target cells and NK cells from healthy donor as effector cells	Comparable ADCC for Remsima and Remicade when NK cells from a healthy donor (genotype V/F) were used as effector cells.
Comparison of ADCC activity between Remsima and Remicade using transfected Jurkat cells as target cells and either PBMCs or NK cells from CD patients as effector cells	No differences in ADCC activity were detected using PBMC from CD patients (V/F or F/F genotype). Differences in ADCC with Remsima and Remicade were seen when NK cells from CD patients were used as effector cells. Effect was FcγRIIIa genotype specific; differences were observed with V/V and V/F, but not F/F genotypes.
Comparison of ADCC effect between Remsima and Remicade using transfected Jurkat cells as target cells and whole blood from healthy donor or CD patients as effector cells	No differences in ADCC were seen between various batches of Remsima and Remicade.
Comparison of ADCC between Remsima and Remicade using LPS-stimulated monocytes from healthy donor or CD patient as target cells and PBMC as effector cells	No ADCC activity was seen with Remsima and Remicade when PBMCs from a healthy donor (V/F) or a CD patient (V/F) were used as effector cells and LPS-stimulated monocytes were used as target cells.
Evaluation of Regulatory Macrophage Function: Suppression of T cell proliferation by induced regulatory macrophages in mixed lymphocyte reaction (MLR) assay	Inhibition of T cell proliferation of PBMCs from healthy donors and CD patients was shown to be comparable and dose dependent for Remsima and Remicade.
Evaluation of Regulatory Macrophage Function: Quantitation of the induced regulatory macrophages by FACS analysis	Induction of regulatory macrophages in a 2-way allogenenic MLR using FcγRIIIa genotype matched PBMCs, from either healthy donors or CD patients, was shown to be comparable for Remsima and Remicade.
Evaluation of Regulatory Macrophage Function: Induced regulatory macrophage-mediated wound healing of colorectal epithelium cells	Promotion of *in vitro* wound healing of colorectal epithelial cells by regulatory macrophages from healthy donors and CD patients (induced by Remsima or Remicade) in the MLR assay was comparable.

Only for illustration, complete list available in the EPAR

- No difference in reverse signaling through tmTNFα
  - Induction of apoptosis
  - Blockade of pro-inflammatory cytokine production
- No difference in blocking soluble hTNFα in an *in vitro* IBD model
  - Suppression of pro-inflammatory cytokine (IL-6 and IL-8) secretion from co-stimulated epithelial cell line
  - Suppression of epithelial cell line apoptosis
- No difference in Complement-dependent cytotoxicity (CDC) activation

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Clinical impact of the difference in FcγRIIIa binding?

- No difference in Regulatory Macrophage function (regMø)
  - Quantity of induced regulatory macrophages, suppression of T cell proliferation, *in vitro* wound healing
- No difference in Antibody-dependent cell-mediated cytotoxicity (ADCC) using
  - tmhTNFα-Jurkat cells as target cells and PBMCs (from healthy donors or CD patients), NK cells (from healthy donors) whole blood (from healthy donors) as effector cells
  - LPS-stimulated monocytes (from healthy donors or CD patients) as target cells and PBMC as effector cells

❖ Difference in ADCC functional assay detected using
  - tmhTNFα-Jurkat cells as target cells and NK cells from CD patient donors (158V/V or 158V/F genotypes, but not 158F/F) as effector cells

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Conclusion from the Remsima assessment

The CHMP concluded that the differences detected were not clinically meaningful;

- Functional difference was seen only in an ADCC assay employing artificially high tmTNFα expressing Jurkat target cells in combination with highly purified NK effector cells
- No differences in experimental models regarded as more relevant to the pathophysiological conditions in CD patients
- No published reports describing the induction of ADCC by TNF antagonists in CD patients
- No firm evidence that the FcγRIIIa polymorphism has an impact on the clinical course of CD

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Biosimilars – prerequisites for extrapolation

- Similar physicochemical, structural characteristics and biological functions in *in vitro* models
- Similar human pharmacokinetics (exposure)
- Similar pharmacodynamics, efficacy, safety, and immunogenicity at least in one therapeutic indication[1]
- Sound scientific justification
  - Clinical experience and available literature data
  - Mechanism of action of the active substance in each indications
  - Evidence that the lead indication is representative for the other therapeutic indications, both with regard to safety and efficacy

➢ Thorough physicochemical and biological characterisation is a prerequisite and a foremost important enabler for succesful extrapolation of similarity data from one indication to another

[1]*For very simple biologics, safety and efficacy studies may not always be necessary*

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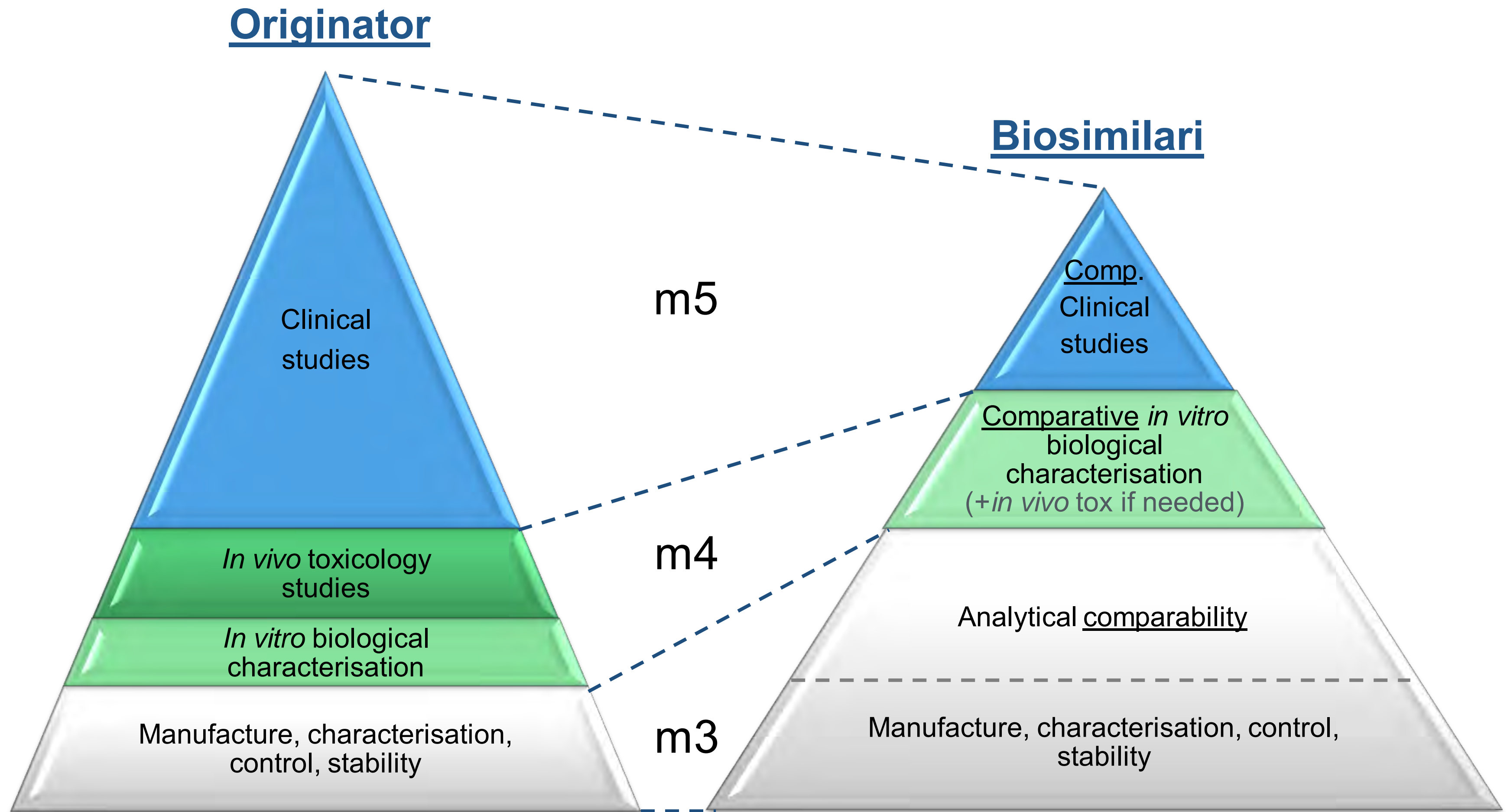
Summary - Marketing Authorisation Application



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Thank you for your attention!

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

Biosimilar guidelines
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c

Remsima EPAR (European public assessment report)
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002576/human_med_001682.jsp&mid=WC0b01ac058001d124

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