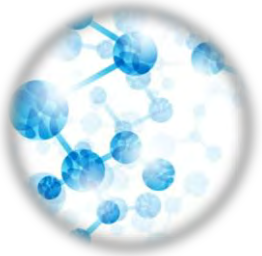

Thijs J Giezen, PharmD, MSc, PhD
The Netherlands

- Hospital Pharmacist, Foundation Pharmacy for Hospitals in Haarlem, The Netherlands
- Member of the Biosimilar Medicinal Product Working Party of European Medicines Agency

First INVIMA Educational Workshop on Assessment of SIMILAR BIOTHERAPEUTIC PRODUCTS

14 June 2016, Hilton Bogotá, Colombia

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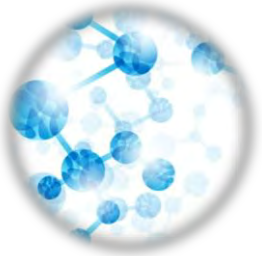
- Member of CHMP Biosimilar Medicinal Product Working Party of European Medicines Agency, London, UK
- Expert at the Medicines Evaluation Board, NL

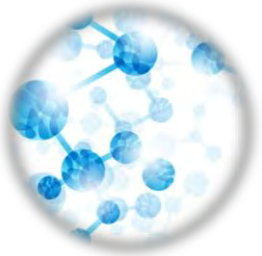
"I attend this conference as an individual expert, and do not represent the CHMP/BMWP. The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the CXMP/WP/SAG or reflecting the position of the CHMP/BMWP."



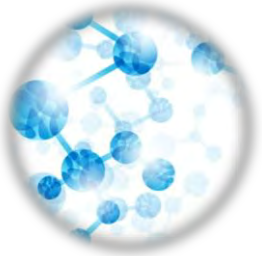
Safety assessment and risk management of biosimilars

Thijs J Giezen, PharmD, MSc, PhD

14 June 2016



Safety of biologicals



Safety of biologicals: a classification

- **Exaggerated pharmacology*:***
  - TB with TNF-alfa inhibitors
  - PML with natalizumab
  - High HB with epoetins
- **Immunological reactions:**
  - Neutralizing antibodies
  - Hypersensitivity reactions
  - Anaphylactic reactions

GaBI Educational Workshops

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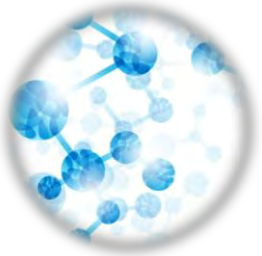
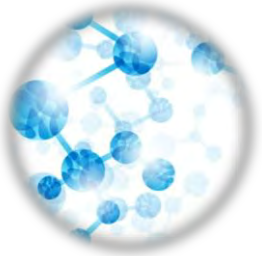


Clinical safety during biosimilar development

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

PPCI
Pro Pharma Communications International



Collection of clinical safety data

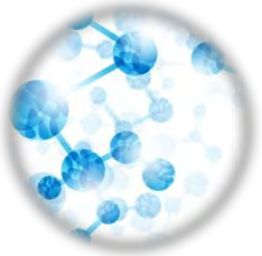
Safety data should be collected during the complete clinical development program

and

should be comparable between biosimilar and reference product

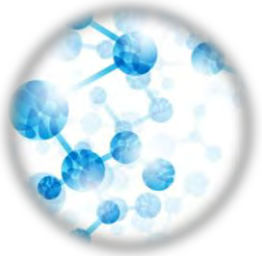
However, clinical trials contain a limited number of patients

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf



Exaggerated pharmacology

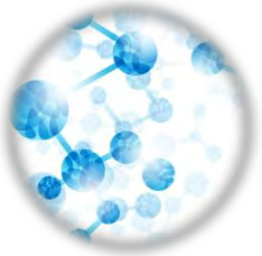
- Safety data should be comparable
- Differences might preclude approval as a biosimilar
- Safety profile of the reference product is the basis
- Highly unlikely that “new” adverse events will emerge for the biosimilar
- Compare adverse events in terms of type, severity and frequency



Exaggerated pharmacology: example

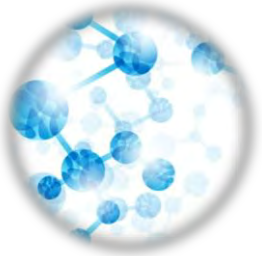
- Higher incidence of serious infections in pivotal clinical trial biosimilar infliximab

- Difference assessed as chance finding:
  - No adequate diagnosis and/ or had pre-existing lesions in 4 cases
  - Total rate of infections was similar
  - No mechanistic explanation



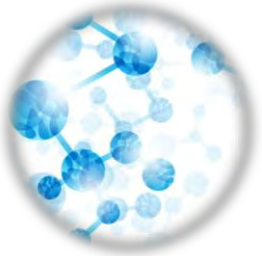
Immunogenicity assessment (I)

- Starts already during quality assessment
- Important during clinical development
- Studied in a comparable manner in sensitive population



Immunogenicity assessment (II)

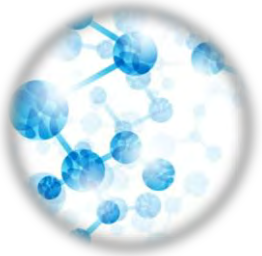
- Number of data based on experience with reference product and/ or product class
- Duration of immunogenicity study should be justified
- Assessed in relation to clinical efficacy and safety



Immunogenicity assessment: example

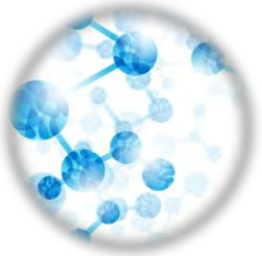
- Infliximab:
  - Antibodies is related to hypersensitivity/ infusion related reactions

- Found in both treatment arms



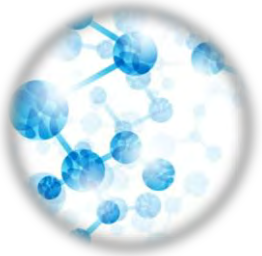
Immunogenicity: an exemption

- Lower immunogenicity for biosimilar might be acceptable
  - Could erroneously suggest more efficacy for biosimilar
  - Subgroup analysis is advised to preclude higher efficacy

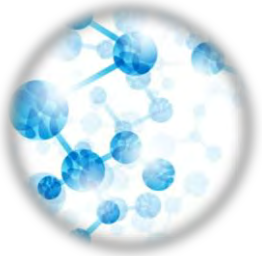


Extrapolation of indication

- Safety should also be considered
- AEs related to exaggerated pharmacology will apparently be similar
- Immunogenicity might differ between indications: justification is needed



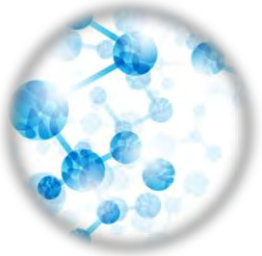
Pharmacovigilance and risk management



Pharmacovigilance

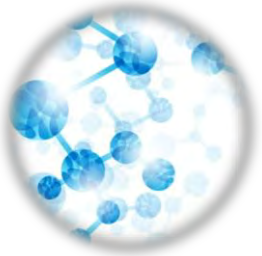
Same rules apply to biosimilars as to all biologicals and new chemical entities

- Biosimilar companies should:
  - Submit a risk management plan as part of the marketing application
  - Collect spontaneously reported adverse events
  - Submit Periodic Safety Update Reports



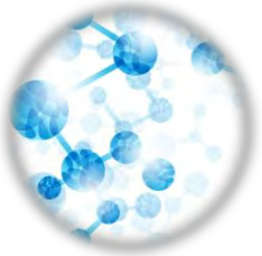
Risk Management Plan of biosimilar

RMP of biosimilar should be based on knowledge and experience obtained with the reference product



Safety specification infliximab biosimilar

- ***Important identified risks:***
  - Haematological reactions
  - Tuberculosis
  - Paediatric leukaemia
  - Leukaemia
- ***Important potential risks:***
  - Colon carcinoma
  - Skin cancer
  - Pregnancy exposure
- ***Missing information:***
  - Long term safety in children
  - Lack of efficacy



Pharmacovigilance plan of a biosimilar

Post-marketing studies not only to compare safety profile but also to learn from rare adverse events

- Participate in already existing studies; e.g. rheumatology registries
- Initiate studies at companies' own discretion

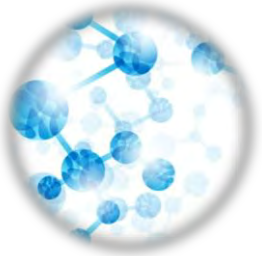
Study
Study CT-P13 1.2: A randomized, double-blind, parallel-group, Phase 1 study to evaluate the initial pharmacokinetics, efficacy, and safety of CT-P13 compared with Remicade when co-administered with methotrexate in patients with active rheumatoid arthritis (Philippines)
Study CT-P13 1.3: An open-label, single-arm, extension study to demonstrate long-term efficacy and safety of CT-P13 in patients with ankylosing spondylitis who were treated with Infliximab (Remicade or CT-P13) in Study CT-P13 1.1 (Global)
Study CT-P13 3.2: An open-label, single-arm, extension study to demonstrate long-term efficacy and safety of CT-P13 when co-administered with methotrexate in patients with rheumatoid arthritis who were treated with infliximab (Remicade or CT-P13) in Study CT-P13 3.1 (Global)
Study CT-P13 3.3: Phase 3study to demonstrate equivalence in efficacy and safety of CT-P13 Compared With Remicade when co-administered with methotrexate in patients with active rheumatoid arthritis (Russia)
Study B1P13101: Double-blind, Parallel-group, Comparative study of CT-P13 and Remicade in Treatment of Patients with Rheumatoid Arthritis (Japan)
British Society for Rheumatology Biologics Register – Rheumatoid Arthritis (BSRBR-RA): A longitudinal observational study of patients with rheumatoid arthritis treated with biologic and other new advanced targeted therapies (UK)

Risk minimisation activities for a biosimilar

Risk minimization activities in place for the reference product also applies to the biosimilar

Unless:

Risk minimisation activity is related to the device by which the reference product/biosimilar is administered



Safety concern	Proposed risk minimisation activities (routine and additional)
Important Identified risks	
HBV reactivation	Routine: Labelling Additional: - Patient Alert Card - Educational material for HCPs
Opportunistic infections	Routine: Labelling Additional: - Patient Alert Card - Educational material HCPs
Serious infections – including sepsis (excluding opportunistic infection and TB)	Routine: Labelling Additional: - Patient Alert Card - Educational material HCPs

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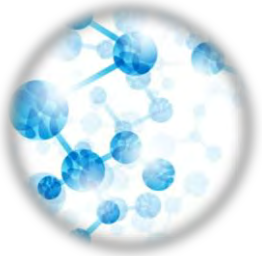

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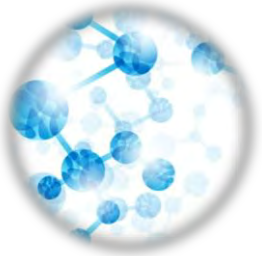
Biosimilars in clinical practice



Biosimilars in clinical practice

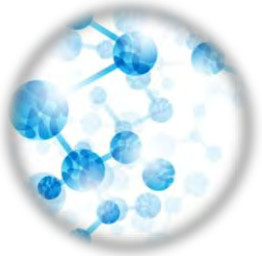
- Traceability:
  - Product responsible for AE
  - Important for all biologicals
  - Challenges remain

- Switching
  - Emotions are involved
  - What is the evidence?

Some definitions

- **Switching**: Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment
- **Substitution**: Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber

GaBI Journal. Ebbers et al. Interchangeability. An insurmountable fifth hurdle. 2014;3(2):88-93



Switching the evidence (I)

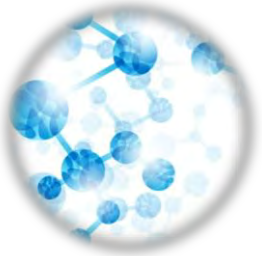
Drug	Number of studies	Number of patients
hGH	*12*	*401*
ESA	35	11.249
GCSF	*10*	*374*
Total	**57**	**12.024**

Expert Opin Biol Ther (2012) 12 (11):1473-1485

Switching the evidence (II)

- 98 patients switched from originator rhGH to Omnitrope
- No negative impact on clinical efficacy based on prediction models
- No reports of serious or unexpected adverse drug reactions
- 18 patients experience pain at injection site, 6 patients switched back to originator

Biol Ther (2013) 3:35–43

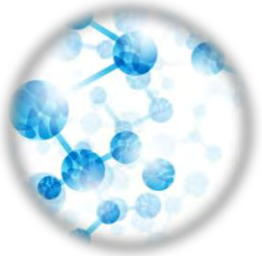


Switching the evidence (III)

- After one year RA and ankylosing spondylitis studies
  - 246 patients continuously treated with Inflectra
  - 230 patients switched from Remicade to Inflectra
  - Similar clinical efficacy at weeks 78 and 102
  - Comparable safety profile

Open-label extension study of the PLANETRA study

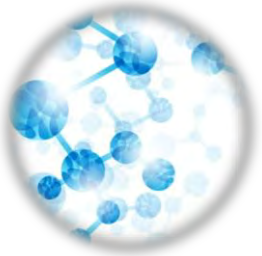
Park W, et al. Ann Rheum Dis 2016;0:1–9. doi:10.1136/annrheumdis-2015-208783
Yoo DH, et al. Ann Rheum Dis 2016;0:1–9. doi:10.1136/annrheumdis-2015-208786



Switching the evidence (IV)

- Phase III trial of Abasria (insulin glargin)
- Limited number of patients switched from Lantus to Abasria
- Significant higher level of antibodies in the switch group compared to the continuous Lantus users
- However, antibody levels were low and no negative impact on efficacy and safety

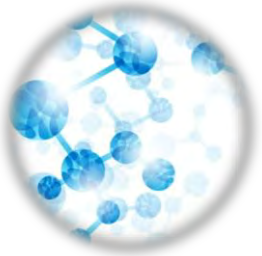
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002835/WC500175383.pdf



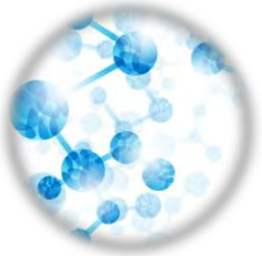
Switching: the evidence

- Studies do not show safety problems

- In clinical practice switching occurs:
  - Reference product <——> reference product due to tenders in hospitals
  - Intravenous <——> subcutaneous

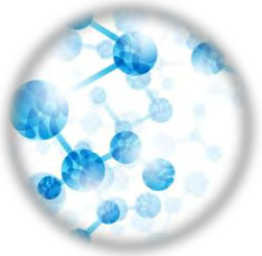


Concluding remarks



Concluding remarks

- Safety assessment is important and should be comparable
- Immunogenicity is of special importance
- Differences might question biosimilarity
- Extrapolation should be justified
- Switching at population level is safe



Concluding remarks

Biosimilars can safely be used in clinical practice