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GaBI Scientific Meetings

ROUNDTABLE ON BIOSIMILARS
with participation by European Regulators and Medical Societies

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Safety assessment and risk management of biosimilars

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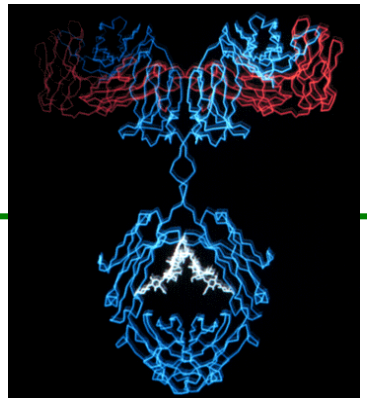

Safety assessment and risk management of biosimilars

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"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."

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Safety of biologicals: a classification

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Safety of biologicals: a classification

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

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Safety assessment during clinical biosimilar development

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Collection of safety data pre-approval

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

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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

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Exaggerated pharmacology: an 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

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Immunogenicity assessment (I)

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

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Immunogenicity assessment (II)

- Number of data based on experience with reference product and/ or product class
- Generally one year for chronically administered products
- Assessed in relation to clinical efficacy and safety

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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

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Pharmacovigilance of biosimilars

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Pharmacovigilance of biosimilars

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

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Risk management plan of a biosimilar

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

Immunogenicity and infusion-related reactions should specifically be included as either a potential or identified risk

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Safety specification infliximab biosimilar

Important identified risks:

- HBV reactivation
- 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

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Pharmacovigilance plan of a biosimilar

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

- Additional immunogenicity studies if considered necessary
- Participate in already existing studies; e.g. rheumatology registries
- Initiate studies at companies own discretion

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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)

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Risk minimisation activities

Conditional approval
(annual confirmation of benefit/risk)

Restriction of indication
(SmPC section 4.1)

Patient alert card

Warnings in the SmPC
(Section 4.4)

Specialised centres
Educational programmes

Systematic risk analysis by registries, PASS,…

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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

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Risk minimisation

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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Labels have a black triangle in the EU

▼ ***„This medicinal product is subject to additional monitoring"***

Medicines with a black triangle are under more stringent control

The black triangle does not mean that biosimilars are less safe

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Traceability of biologicals

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Traceability of biologicals

Traceability is of high importance for all biologicals

Adverse events should be reported based on brand name and batch number

(e) ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number;

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Traceability: current situation

	FAERS	EV
Total # ADR reports	2,028,600	2,108,742
# ADR reports biopharmaceuticals suspected	487,065	356,293
% reports batch numbers available	24%	21.1%
# ADR biosimilar approved	NA	9,759
% reports brand name available	NA	96.2%
% reports brand name and batch # available	*NA*	*5.7%*

Vermeer et al. Drug Safety 2013;36(8): 617-25

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Traceability: current situation in the EU

- Drugs prepared by the hospital pharmacy => information on brand name and batch number is collected on the protocol
- Prefilled syringes administered in the hospital => barcode controlled administration
- Prefilled syringes administered by the patient at home => barcode controlled delivery to the patient

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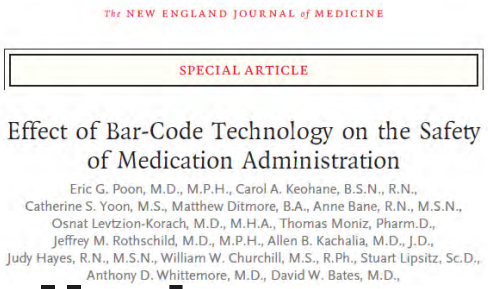

Traceability: barcode controlled administration

- Current barcodes are linear barcodes and hold information on the National Trade Item Number (NTIM)
- NTIM is unique to manufacturer, dosage form and strength of a product
- However, batch number is not included in NTIM

Vermeer et al. Expert Opin Drug Saf 2015;14(1): 63-72

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Concluding remarks

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Concluding remarks

- Safety assessment is important and should be comparable
- Immunogenicity is of special importance
- Differences might question biosimilarity
- Pharmacovigilance is important as for all drugs
- Traceability is of specific importance for all biologicals