Hot Topics in Oncology: Biosimilar Monoclonal Antibodies

Pharmacovigilance

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Pharmacovigilance/Risk Management Plan

"…is to be presented in accordance with current EU legislation and pharmacovigilance guidelines"

- In order to study safety in the post-authorisation setting
- Safety in extrapolated indications, long-term safety data
- Additional immunogenicity data, if considered
- Proactive pharmacovigilance activities, e.g. registries
- Adverse reaction report with name and batch number
- Switching and interchanging

EMA Guideline on Similar Biological Medicinal Products containing monoclonal Antibodies CHMP/BMWP/403543 2010

Case study: Remsima Pharmacovigilance Plans (excerpt)

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)	1.0	Final	Interim analyses will be undertaken at appropriate time intervals. Such analyses will be a guide to the ultimate levels of recruitment and length of follow-up required Annual Special Interest report (TB and other serious infection) with PSUR Pooled TB and other serious infection registry analysis to be submitted in December 2017 (with any data available at the data cut off point of 3100 patients)	March 2026
Registry CT-P13 4.3: An observational, prospective cohort study to evaluate the safety and efficacy of Remsima in patients with Crohn's disease (CD), and Ulcerative Colitis (UC) (EU and Korea)	Synopsis	Draft	Annual Safety and Efficacy Interim Analysis (data cut off December; reporting May) Annual Special Interest report (TB and other serious infection) with PSUR Pooled TB and other serious infection registry analysis to be submitted in December 2017 (with any data available at the data cut off point of 3100 patients)	May 2026

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 May 2012
EMA/CHMP/BMWP/86289/2010
Committee for Medicinal Products for Human Use (CHMP)

Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use.

Revision under consultation

- Comparative immunogenicity studies
- Post licensing immunological studies

Case study: Remsima CT-P13

Remsima Assessment report EMA/CHMP/589317/2013

- **Uncertainty in the knowledge about beneficial effects**
  There is a slightly higher level of aggregates in the CT-P13 product than in Remicade, which could potentially increase immunogenicity. However, the risk is considered to be negligible given the very low level and is not reflected in the clinical data.
- **Risks**

  There were no marked differences in the immunogenicity profile of CT-P13 and Remicade up to 54 weeks and the impact of antibodies on efficacy and safety was comparable

Traceability and Naming

- ***For accurate pharmacovigilance, both brand name and INN should be recorded when prescribing[1]***
- ***Physician would be well advised to always document exactly which biological is used for an individual patient. In the ADR report ….INN, brand name, manufacturer, lot number, country of origin to ensure a proper root cause analysis[2]***
- ***For suspected adverse reactions ….. the definite identification of the concerned product with regard to its manufacturing is of particular importance. Therefore, all appropriate measures should be taken to identify clearly any biological medicinal product ….. with due regard to the name … and the batch number[3]***

1. Declerck P. *Drug Safety* 2007;30:1087-92; 2. Ehmann, F., Schneider K. HPE 2011;56:32-35,
3. EMA Guideline on Similar Biological Medicinal Products containing monoclonal Antibodies CHMP 403543 2012

How similar is similar ?

- **Similarity**
  - Products of different manufacturers
  - Similar to the reference product in quality, efficacy (therapeutic equivalence), tolerability (EMA)
  - Not meaningfully different from the reference product in terms of safety, purity and tolerability (FDA)

- **Comparability (ICH Q5E)**
  - Product of the same manufacturer
  - Exercise to ensure the quality, safety and efficacy of a biological product subject to changes in the manufacturing process (pre- / post-change)

Interchangeability of Biosimilars

- Interchangeability: Exchange of one medicine for another expected to achieve the same clinical effect in a given clinical setting

- ***Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional.[1]***

- ***It is not possible we would guarantee a biosimilar is interchangeable (with its originator) and substitution is a national competency and needs to be discussed at the national level[2]***

1. London, 19 April 2007 Doc. Ref. EMEA/74562/2006; 2. EMEA Executive Director Thomas Lönngren 2006

Substitution of Biosimilars

- **Substitution**
  Refers to a national policy which permits the switch from one to another medicine that has been demonstrated to have the same quality, safety and efficacy
- Automatic substitution typically occurs at **retail or hospital pharmacies without consulting the prescriber**

- ***Depending on the handling of biosimilars and reference medicinal products in clinical practice at national level, 'switching' of medicines that contain a given mAb might occur. Thus applicants are recommended to follow further development in the field and consider these aspects as part of the risk management plan.***

Guideline on Similar Biological Medicinal Products containing monoclonal Antibodies CHMP/BMWP/403543 2010

12.Is switching between a reference medicine and a biosimilar medicine (and vice versa) safe?

There is relatively little published data available on the number of patients that have been switched between biopharmaceuticals in clinical practice. "*For questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist*"[42].

[42] See question: Can a biosimilar medicine and its reference medicine be used interchangeably? in EMA/837805/2011_Questions and answers on biosimilar medicines (similar biological medicinal products)_September 2012

27 September 2012
EMA/837805/2011

Questions and answers

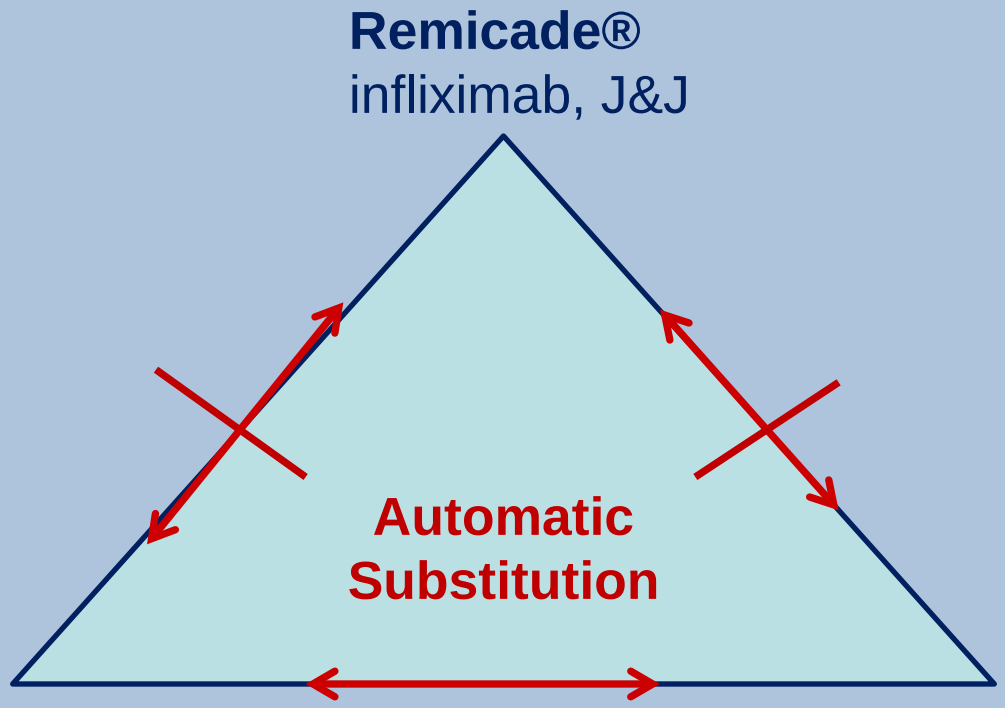
Questions and answers on biosimilar medicines (similar biological medicinal products)

Can a biosimilar medicine and its reference medicine be used interchangeably?

The EMA evaluates biosimilar medicines for authorisation purposes. The Agency's evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. For questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist.

Substitution of Biosimilars in Germany

- Automatic substitution of biosimilars not allowed
- Automatic substitution of bioidenticals allowed
- **Example**



Risk management of Biosimilars in hospital practice

Substitution/switching should be combined with

- Close monitoring of the patients
- Ensured traceability
- Decision making by a qualified healthcare professional

Risk management of Biosimilars in hospital practice

- Use in extrapolated indications especially challenging with regard to mAbs
- Different post marketing commitments for different indications
- Different patient groups (treatment naïve, multiple switching)

- Information of the P&T committee, physicians about RMPs by hospital pharmacists
- Consensus decision with responsible physicians
- Additional workload, additional awareness