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# European medical societies' position papers on biosimilars: concerns and controversies

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## **Roundtable on Biosimilars with participation by European Regulators and Medical Societies**

# European medical societies' position papers on biosimilars: concerns & controversies

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## Scope

Many position papers and guidelines have been issued by medical societies on the use of biosimilars

- Included
  - Recent position papers
  - Focusing on monoclonal biosimilars
- Excluded
  - Papers without English translation
  - Old position papers on biosimilar filgrastims, epoetin alfas and somatropins
- Focus
  - Concerns of the medical societies

## The Portuguese Society of Rheumatology position paper on the use of biosimilars

- **International Position Papers on the use of biosimilar drugs: A systematic literature review**
  - *medical societies,*
  - other non-profit non-governmental organizations,
  - governmental/regulatory organisations,
  - industry associations and individual companies
- **Position papers are increasing**
  - In the same time, biosimilars to blockbuster biologicals, mainly biosimilar mAbs are entering the market
  - Older position papers may be revised

## The Portuguese Society of Rheumatology position paper on the use of biosimilars

- **Results in a nutshell:**
  - All papers were favourable to the use of biosimilars (in principle)
  - Mixed opinions on (automatic) **extrapolation**
  - Concerns about **traceability**, prescribing by brand name favoured
  - Additional safety concerns: **Immunogenicity, unexpected adverse effects**
  - **Interchangeability** accepted if prescribers in charge of switching
  - **Automatic substitution** opposed by many organisations

## Position papers of European Medical Societies (in English)

- **Medical Societies in the Portuguese survey**
  - European Crohn's and Colitis Organization, 2013
  - Sociedad Española de Patología Digestiva / Sociedad Española de Farmacología , 2013
  - Austrian Society of Hematology and Oncology, 2008
  - Italian Society of Hematology. 2011
  - Société Française de Néphrologie/ Société Francophone de Dialyse, 2009

## New position papers on the use of biosimilars by medical societies

- Position document of the **Belgian** IBD Research & Development Group (BIRD), 2015
- **British** Society for Rheumatology Position statement on biosimilar medicines, 2015
- The use of biosimilars in immune-mediated disease: A joint **Italian** Society of Rheumatology (SIR), Italian Society of Dermatology (SIDeMaST), and Italian Group of Inflammatory Bowel Disease (IG-IBD) position paper), 2014
- **EULAR** recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update



## Main topics and worries

- Comparability and biosimilar development
- Extrapolation of safety and efficacy
- Role of clinical trials
- Switching, interchangeability and automatic substitution
- Pharmacovigilance and risk management

## Comparability and biosimilarity

- Due to the complex manufacturing process and highly intricate structure of biologicals, a biosimilar can never be an **exact copy** of its reference product
- It is unlikely that a **perfectly identical molecule** can be recreated from the reference product
- **Any uncertainties**, such as **slight differences of unknown relevance** to clinical performance, should be addressed via comparative clinical data.
- However it is important to realize that biosimilars have a proven similarity without being identical to the reference product. Therefore as physicians we have concerns about the efficacy and safety of the biosimilars. Direct evidence of safety and benefit from clinical trials in IBD is needed
- Even sophisticated comparability testing, **in vitro assays and animal studies cannot fully predict the biological and clinical activity of a therapeutic monoclonal antibody.**

## Extrapolation of safety and efficacy

- Extrapolation of indications approved for the originator drug to **completely different diseases and age groups** that are not based on adequate pre-clinical, safety and efficacy data (ideally phase I and phase III trials) should not be performed
- Extrapolation from **rheumatoid arthritis and ankylosing spondylitis studies to Crohn's disease and/or ulcerative colitis** cannot be done. Information on **mucosal healing, corticosteroid-free remission or immunogenicity and loss of response in CD or UC patients is needed.**
- **The mode of action** of infliximab may be different in the different diseases.
- The same concerns apply also to **paediatric patients. Studies specifically looking at some paediatric outcomes** such as growth and development are welcomed.

## Extrapolation of safety and efficacy

- The equivalence clinical trials for each biosimilar are conducted within a **small trial population** and **no clinical trial is undertaken for each licensed indication** of the reference products, weakening the evidence used to support extrapolation of indications from reference treatments
- **EMA recommendations** on a possible extension of indications to areas not directly researched **are anyway inconclusive**; while a door remains open to this possibility, it is only considered for cases based on **sound scientific reasoning**.
- In no case does a license obtained for the management of a certain disease allow an extrapolation of results to a different disorder. **As with originals, in order to obtain a given indication a biosimilar should be tested in a clinical trial specifically designed to that end.**

## Role of clinical trials

- Lack of knowledge of **the long term safety of biosimilar drugs** which may have subtly **different immunogenic profiles**.
- The **clinical trials** (of biosimilars) have been of **new users only**, with no trial of direct substitution from an originator drug for rheumatological or autoimmune diseases. This is significant, as biosimilar medicines will be available for use at **many different points along the treatment pathway**, including as first biologic, subsequent biologic after previous failure and, for the first time, as a substitute biologic for patients who are well controlled on a reference agent.

## Switching, interchangeability, and automatic substitution

- **Biosimilarity does not imply that the drugs are interchangeable**
- **When switching between biosimilars and the originator molecule, safety and efficacy assessments must be performed and patients registered**
- **Switching** between biosimilars and the originator molecule should be done after **at least 6 months of treatment** and based on the attending physician decision and after adequate patient information
- It is **important that physicians maintain control over prescribing** these products and **financial pressure alone should never become the driver for the decision**
- There are no data about cross-linking anti-drug antibodies (in IBD), one cannot advise on the safety of starting biosimilars in IBD patients with prior use of infliximab or in patients with infusion reactions to infliximab

## Switching, interchangeability, and automatic substitution

- Furthermore, there appears to be **little evidence of the safety and effectiveness** of switching to biosimilars in patients who are stable on a reference agent.
- **The inclusion of biosimilars as a biologic therapy choice for patients initiating a new biologic therapy is supported** but universal mandate that all patients should start a biosimilar purely to save costs is not supported
- The decision to **switch should be on a case-by-case** basis and until further data are available to support safe switching
- **Strong safeguards are required to ensure that patients who have responded well to existing medicine are not switched for non-clinical reasons.**

## Switching, interchangeability, and automatic substitution

- Until further data become available, these products should not be considered globally interchangeable. **The patient must be kept informed at all times of the discussions taking place in regard to their medicine.**
- **Substituting a biosimilar for the original drug cannot be an accepted practice**
- It is self-evident that an infliximab biosimilar cannot be regarded as ‘another TNF inhibitor’ in patients with an insufficient response to infliximab



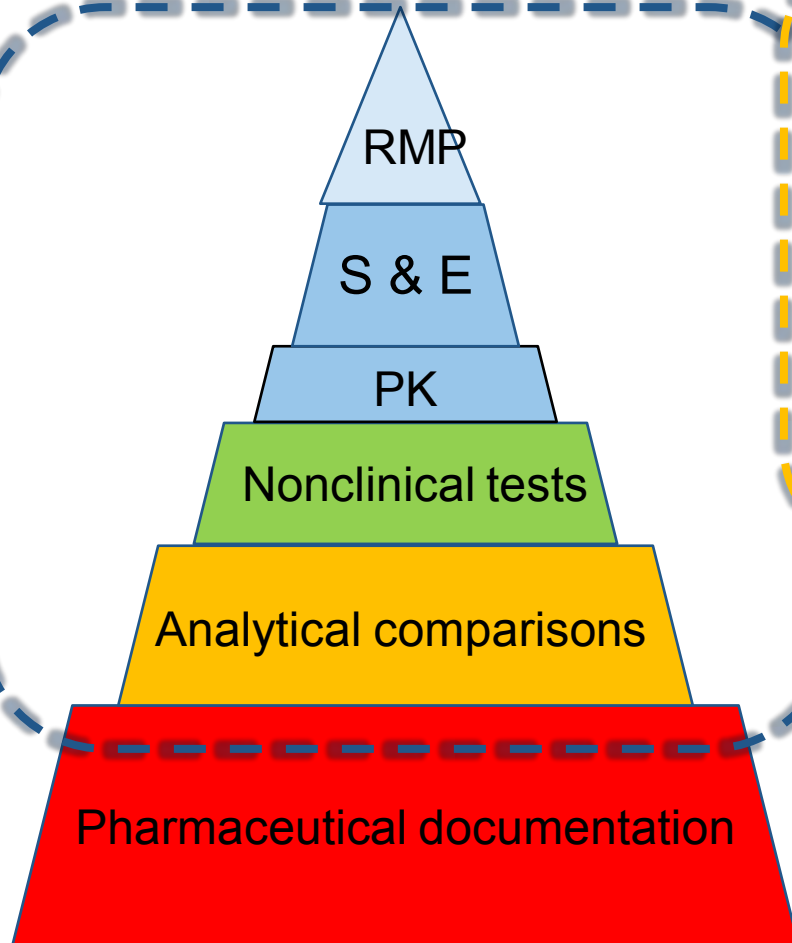
## Pharmacovigilance and risk management

- Biosimilars should have a **different INN** or be prescribed by **brand name**
- Patients with biosimilars should be followed in a **register**
- **Immunogenicity evaluation should be performed when clinically relevant and available**. As laboratory methods of assessing immunogenicity are not routinely available in clinical practice, **immunogenicity must be inferred from the adverse events and secondary loss of efficacy** data reported in the register and this information should be reported to health authorities;
- **It is best practice to record data on all patients starting biosimilars in a consistent and systematic way and to monitor adverse events over the long term.**

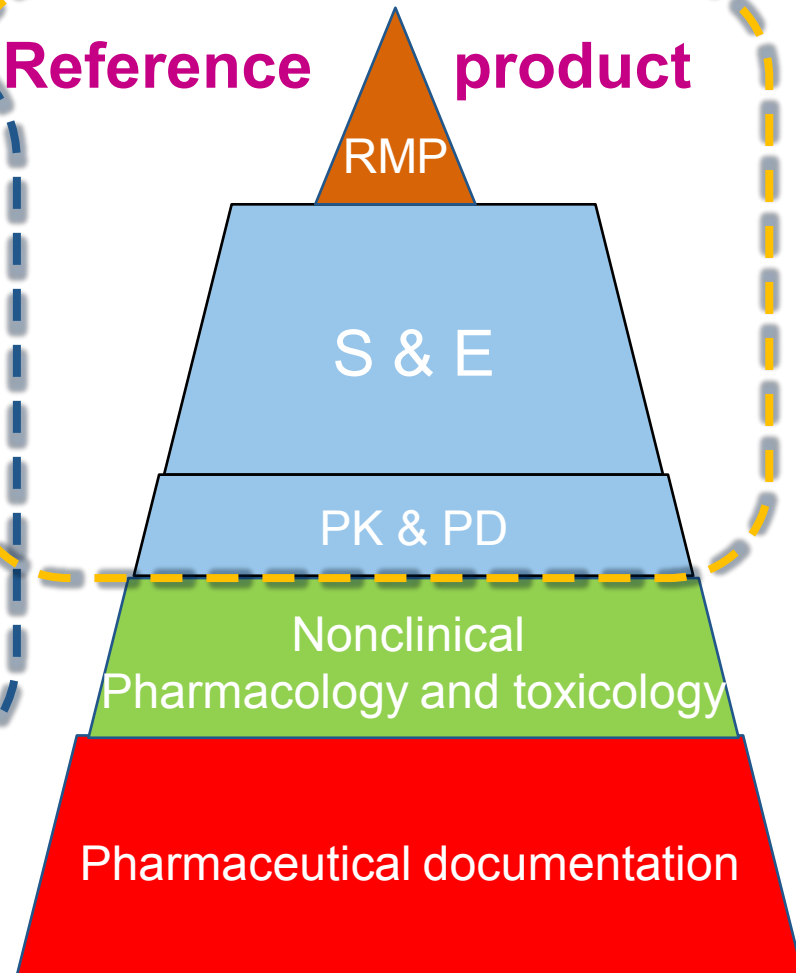
# Conclusions and topics for Discussion

## Different development philosophies

### Biosimilar

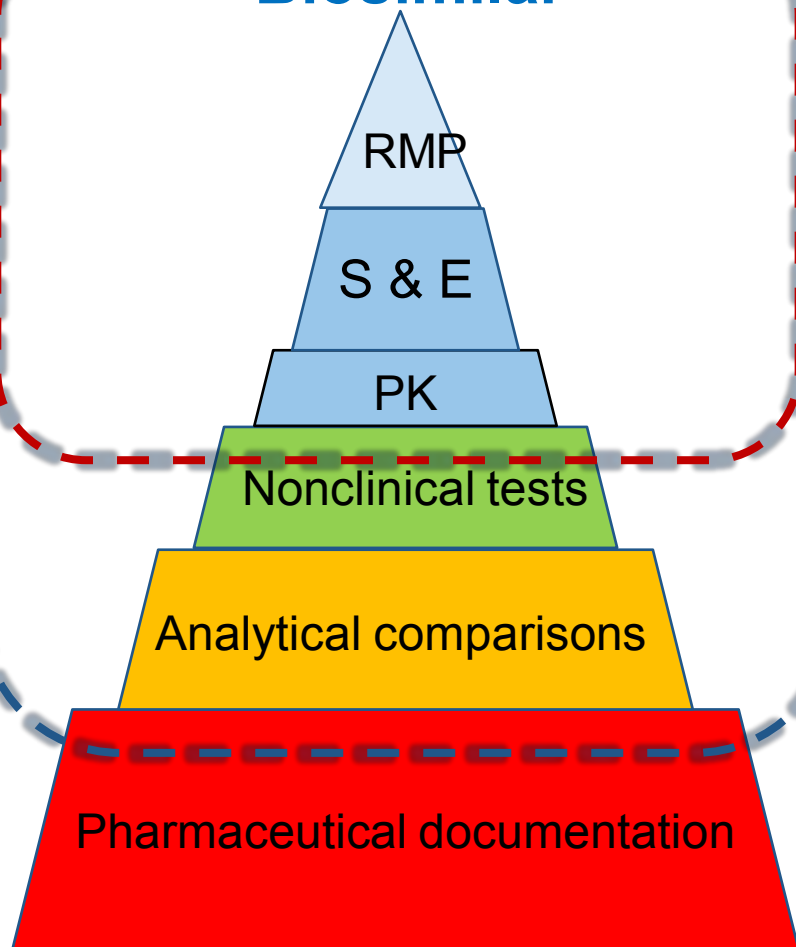


### Reference product



## Regulators and clinicians have different viewpoints

### Biosimilar



- Lack of confidence in comparability
- Reliance on the experience gained from manufacturing changes
- Confidence in clinical trials
- Clinical trials as a part of the comparability (totality of evidence)
- Biosimilar is a new product
- Biosimilar contains a new version of the active substance of the reference product
- Pathogenesis is important
- Receptor binding is important

## Possible topics for discussion

- Comparability and biosimilar development
  - Can the experience from manufacturing changes be used to evaluate biosimilars
  - What is meant by an “exact copy” and “identical”
  - Understanding the impact of differences
- Role of clinical trials
  - Lack of knowledge of the long term safety of biosimilar drugs which may have subtly different immunogenic profiles. How to address such a problem?
  - How to choose the population/disease for a comparative clinical trial?
  - Endpoints and study designs

## Possible topics for discussion

- Extrapolation of safety and efficacy
  - Role of the pathogenesis of the disease
  - Role of the mode of action of the active substance
  - Which are relevant arguments for and against extrapolation
- Switching, interchangeability
  - Switch between a biosimilar and its reference: How, when and in whom
  - How can a switch cause problems?
  - Should every biosimilar be tested in a clinical switch trial
  - How to do a switch study?

## Possible topics for discussion

- Pharmacovigilance and risk management
  - Registers (for biosimilars)
  - Immunogenicity post-marketing
  - Traceability

*Thank you for your attention*