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GaBI Scientific Meetings

2nd MENA Stakeholder Meeting on **Regulatory Approval, Clinical Settings, Interchangeability and Pharmacovigilance of Biosimilars**

10 October 2018, Le Meridien Dubai, United Arab Emirates

Regulation of biosimilars in the EU – immunogenicity

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10 October 2018

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GENERICS AND BIOSIMILARS INITIATIVE
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Biosimilars - EMA Definition

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.

Biosimilars - EMA Legal Basis

A company may choose to develop a biological medicinal product claimed to be “similar” to a reference medicinal product, which has been granted a marketing authorisation in the European Economic Area (EEA) on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended.

Biosimilars in the EU

Biosimilars are now firmly established in the EU as copy biologicals with a clear and effective regulatory route for approval, which allows marketing of safe and efficacious biosimilar products.

Biosimilars - Comparability

Comparability studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the similar biological medicinal product and the chosen reference medicinal product authorised in the EEA.

CHMP has produced several guidelines describing what is necessary from the regulatory perspective for biosimilars.

Principles of establishing biosimilarity

A biosimilar should be highly similar to the reference medicinal product in physicochemical and biological terms. Any observed differences have to be duly justified with regard to their potential impact on safety and efficacy.

Unwanted Immunogenicity

Current Position

Testing for unwanted immunogenicity is integral to product development (clinical & post-marketing phase) for ensuring:

- The clinical safety of a biotherapeutic
- Product Comparability
- When a Biosimilar product is developed

Unwanted Immunogenicity

- Biological products (including biosimilars) can induce antibodies with different characteristics:
  - Non-neutralizing (binding) antibodies against active (and/or inactive) product-related substance(s).
  - Binding antibodies against contaminants.
  - Neutralising antibodies.
  - Mixtures of the above.
- But antibodies are not necessarily induced by biologicals/biosimilars. Incidence varies.

Potential Clinical Consequences of immunogenicity

- Can range from benign, non-significant to serious life-threatening depending on the therapeutic
- Consequences on efficacy - reduction of the clinical response to the biotherapeutic
- Consequences on safety- safety issues can occur even when there is no loss of efficacy

Acute consequences

- Infusion reactions, anaphylactic reactions

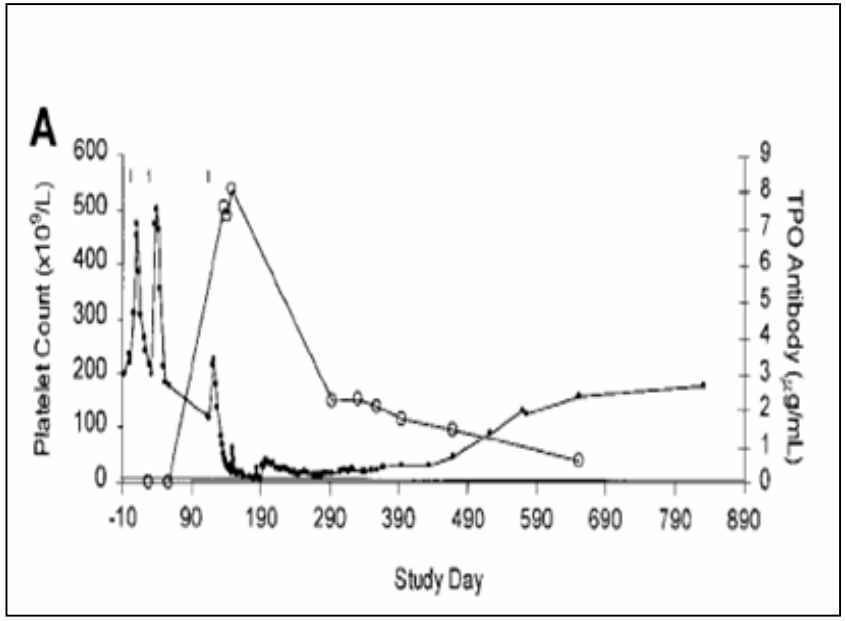
Non-acute consequences

- Delayed-type hypersensitivity/immune complexes
- Cross-reactivity with an endogenous counterpart

Antibodies and Adverse Effects; Classic Examples

MGDF administered to patients caused thrombocytopenia.

- Cancer patients 4/650;
- healthy patients 13/325



Product development terminated

Pure red-cell aplasia (PRCA) and anti-EPO antibodies in patients treated with EPO (EPREX)

- Pre 1998 – 2/3 cases
- 2002 - 13 cases in chronic renal failure patients, rapid development of severe transfusion dependence within months of therapy, resistant to other EPO products
- 1998 to June'05 – 260+ cases worldwide (probably an underestimate).

Cause(s) ?

Casadevall N, et al. *N Engl J Med.* 2002;346(7):469-475.

Factors Influencing Unwanted Immunogenicity

Product and Patient related

- Molecular structure, novel epitopes, glycosylation, degradation, oxidation, deamidation
- Product impurities
- Formulation
- Aggregation
- Protein – biological properties e.g., immunostimulant
- Dose, route, frequency of administration and duration of therapy
- Immune status, age, genetic profile, disease, treatment
- Previous exposure

Unwanted Immunogenicity – The Most Challenging Issues

- It is impossible to predict
  - the incidence of unwanted immunogenicity
  - the characteristics of the immune response
  - the clinical consequences & significance of such immunogenicity
- THE ABOVE NEED TO BE ASSESSED IN APPROPRIATE STUDIES
- These immunogenicity studies are normally carried out as part of clinical trials.

Immunogenicity Testing: A Tiered Approach

Screening assays **–** for 'identification' of <u>all</u> anti-therapeutic antibodies

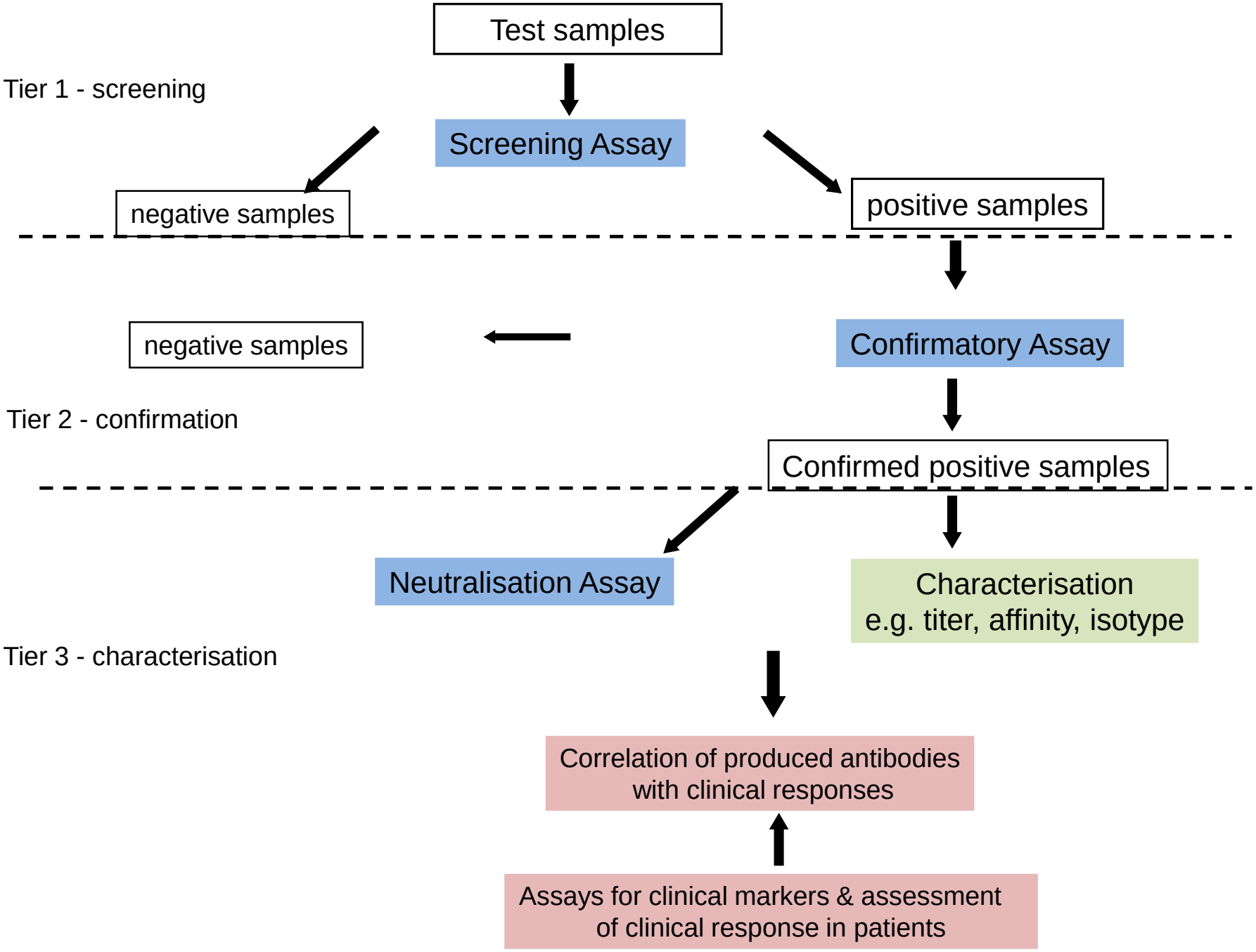
- ELISAs - direct, bridging, other formats
- Radioimmunoprecipitation assays (RIPA)
- Surface Plasmon Resonance (SPR)
- Other technologies

Confirmatory assays - for confirming antibodies

Other assays **–** for specificity of the antibodies

Neutralization assays **–** for discriminating neutralizing & non-neutralizing antibodies.

- Cell- based assay or
- Non-cell-based ligand binding assay


Test samples
Tier 1 - screening
Screening Assay
negative samples
positive samples
negative samples
Confirmatory Assay
Tier 2 - confirmation
Confirmed positive samples
Neutralisation Assay
Characterisation
e.g. titer, affinity, isotype
Tier 3 - characterisation
Correlation of produced antibodies
with clinical responses
Assays for clinical markers & assessment
of clinical response in patients

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 May 2017
EMEA/CHMP/BMWP/14327/2006 Rev 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Immunogenicity assessment of therapeutic proteins

Draft revision agreed by Biosimilar Medicinal Products Working Party (BMWP)	August 2015
Adopted by CHMP for release for consultation	24 September 2015
Start of public consultation	01 October 2015
End of consultation (deadline for comments)	31 January 2016
Agreed by Biosimilar Medicinal Products Working Party (BMWP)	November 2016
Adopted by CHMP	18 May 2017
Date of coming into effect	01 December 2017

This guideline replaces 'Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins' (EMEA/CHMP/BMWP/14327/2006).

Keywords	***Immunogenicity, therapeutic proteins, anti-drug antibodies (ADA), assays, assay strategy, binding antibodies, neutralising antibodies, risk factors, safety, efficacy, pharmacokinetics, risk management, integrated summary of immunogenicity***

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.

Draft agreed by Similar Biological Medicinal Products Working Party	October 2010
Adoption by CHMP for release for consultation	November 2010
End of consultation (deadline for comments)	May 2011
Final agreed by BMWP	March 2012
Adoption by CHMP	24 May 2012
Date for coming into effect	1 December 2012

Disclaimer: This guideline is intended as an addendum to Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins EMEA/CHMP/BMWP/14327/2006 and should be read in conjunction.

Keywords	**Immunogenicity, monoclonal antibodies, similar biological medicinal products, clinical use, assay strategy.**

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Biosimilars: Comparability Concept

Comparability studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product authorised in the Community.

This applies to the immunogenicity assessment.

Comparative Immunogenicity

- Compares immunogenicity of different products ;

  Studies need to be designed to demonstrate whether the immunogenicity of the products is the same or significantly different.
- This is likely to affect the design of the studies & their interpretation.
- For this, a homogeneous and clinically relevant patient population should be selected. Head-to-Head studies needed. Same assays & sampling strategy should be used.
- The consequences of immunogenicity also must be compared.
- Post-approval assessment may be necessary, usually as part of pharmacovigilance surveillance.

Immunogenicity Studies: Biosimilars

The immunogenicity of the marketed product does not influence the need for comparative immunogenicity studies.

However, if the immunogenicity profiles of marketed and biosimilar products are significantly different, they can be considered DISSIMILAR

Unwanted Immunogenicity; what types of Products are affected?

BINOCRIT

Approved – 2007 following rigorous physico-chemical, biological characterisation & clinical trial data
Brockmeyer & Seidl (2009) Biologicals

Safety Study for Binocrit **(Biosimilar EPO) Suspended:**

– No increased immunogenicity from IV use in patients with renal anaemia or SC use in cancer patients (both licensed).

– Postmarketing SC trial in previously untreated renal anaemia patients: two cases of neutralising Ab development. Cause linked to syringe plungers?

PROBLEMS in THAILAND:

> 60 PRCA cases identified in Thailand. 16 EPO (or more) products marketed. Link to product(s) ?

Unwanted Immunogenicity; what types of Products are affected?

- Unwanted immunogenicity is a potential problem for ALL biologicals.
- The clinical implications of unwanted immunogenicity are also potential problems for ALL biologicals.
- This applies to innovator biologicals, biosimilars and non-innovator biologicals.
- It is NOT a specific problem for biosimilars.
- So far, the incidence of unwanted immunogenicity for innovator products and biosimilars is very similar.
- There may be increased immunogenicity problems for some non-innovator biologicals (as used in developing countries), but these products are NOT biosimilars.

Acknowledgements

Meenu Wadhwa

Colleagues of the BMWP

Thank you!

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