Update on guidelines on immunogenicity of monoclonal antibodies and biosimilars

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EMA Activities-Biosimilars

- Since establishment of the biosimilar regulatory framework, there have been significant activities at BMWP level:
  - Biosimilars have been approved; many products are in development (some at late phase), scientific advice given
  - Guidelines – new (drafts in consultation), general GLs (revision stage)
  - Q&A document on Biosimilar Medicines (EMEA/74562/2006 Rev.1) - revision

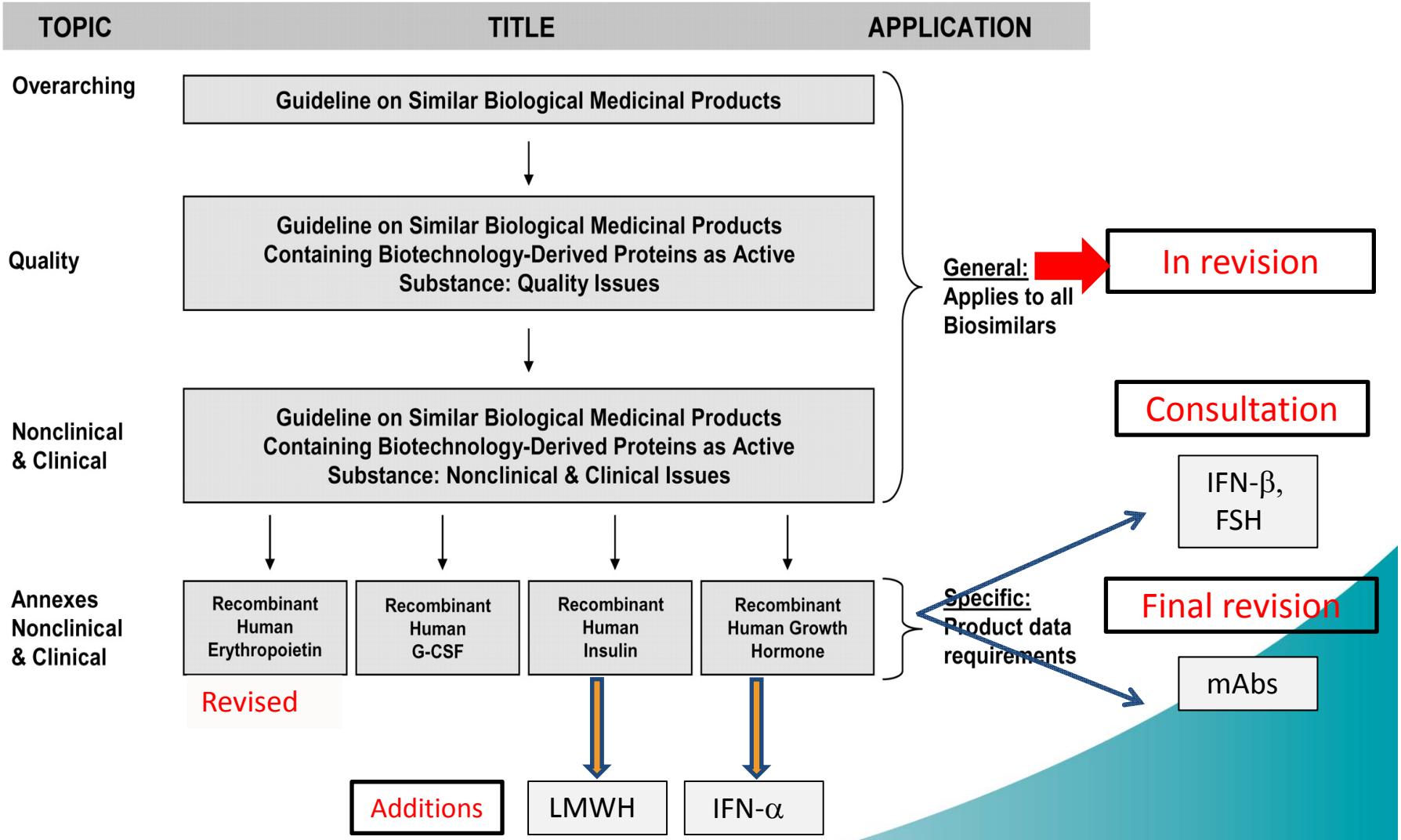
Biosimilars Approved in EU

Product	Company	INN	Reference Product	Date Approved
Omnitrope	Sandoz (owned by Novartis)	Somatropin	Genotropin (Pfizer)	April 2006
Valtropin	BioPartners	Somatropin	Humatrope (Eli Lilly)	April 2006
Binocrit	Sandoz	Epoetin alfa	Eprex/Erypo (Janssen-Cilag)	August 2007
Epoetin alfa Hexal	Hexal Biotech (owned by Novartis)	Epoetin alfa	Eprex/Erypo (Janssen-Cilag)	August 2007
Abseamed	Medice Arzneimittel	Epoetin alfa	Eprex/Erypo (Janssen-Cilag)	August 2007
Silapo	Stada Arzneimittel	Epoetin zeta	Eprex/Erypo (Janssen-Cilag)	December 2007
Retacrit	Hospira	Epoetin zeta	Eprex/Erypo (Janssen-Cilag)	December 2007
Ratiograstim	Ratiopharm	Filgrastim	Neupogen (Amgen)	September 2008
Filgrastim Ratiopharm	Ratiopharm	Filgrastim	Neupogen (Amgen)	September 2008
Biograstim	CT Arzneimittel	Filgrastim	Neupogen (Amgen)	September 2008
Tevagrastim	Teva Generics	Filgrastim	Neupogen (Amgen)	September 2008
Zarzio	Sandoz	Filgrastim	Neupogen (Amgen)	February 2009
Filgrastim Hexal	Hexal Biotech Forschungs GmbH	Filgrastim	Neupogen (Amgen)	February 2009
Nivestim	Hospira	Filgrastim	Neupogen (Amgen)	2010

Alpheon (interferon alfa, being developed by BioPartners) was refused approval in June 2006 and Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel were withdrawn in 2008 (insulin, being developed by Marvel Life Sciences Ltd).

Wadhwa M & Thorpe R. IDrugs 2009 12:440-4.

EMA Guidelines on Biosimilars



European Medicines Agency http://www.ema.europa.eu/, accessed 23 February 2011.

Biosimilar Quality Guideline

- Guideline is being extensively revised by a drafting group comprising members of the BWP & BMWP.
- This takes account of experience gained with quality assessments of approved biosimilars and biosimilars in development e.g. from scientific advice meetings.
- At present is at the advanced drafting stage.
- Has considerable technical detail.
- Does not contain much on immunogenicity.

Other EU Guidelines

- **Guideline on similar biological medicinal products containing monoclonal antibodies -** non-clinical & clinical issues

  'External consultation' over. Revision nearly completed. Mainly concentrates on non-clinical & clinical issues – title altered to reflect this. Provides some (additional) guidance on assessment of comparative immunogenicity.

- **Guideline on Similar Biological Medicinal Products Containing Interferon Beta.**

  'External consultation' currently underway. Contains quite a lot on unwanted immunogenicity. For NAb, recommends MxA assay or NAb assay validated against the MxA assay.

BWP report to CHMP on Beta-IFNs & NAbs

- The MxA protein assay is a suitable standardised test method for measuring neutralizing antibodies.
- If using other methods utilizing updated technologies, it is stressed that the sponsors '*have to demonstrate how the new assay compares to the agreed upon common assay (MxA protein), so as to guarantee standardisation in the expression of the results in antibody formation and incidence rate (to be reported in published literature)'.*

(Excerpt : EMEA/CHMP/BWP/580136/2007)

EMA Guidance

Unwanted Immunogenicity

- Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins
  EMA/CHMP/BMWP/14327/2006
- Guideline on Immunogenicity Assessment of monoclonal antibodies – final revision (following external consultation)
  EMA/CHMP/BMWP/86289/2010

Immunogenicity Guideline

- General Guideline has been generally well received.
- Guideline has been used by manufacturers and regulators.

- One criticism has been that it is ‘too general’, does not deal with specific products.
- It is clearly not possible (or desirable) to write specific guidelines for all products.
- However some product classes may merit more specific guidelines.

New CHMP Guideline

- **There is to be a new CHMP guideline:**

  ‘IMMUNOGENICITY ASSESSMENT OF MONOCLONAL ANTIBODIES INTENDED FOR IN VIVO CLINICAL USE’.
- **Consultation completed/comments received May 2011.**
- **Revision at completion stage.**

Comments from Consultation

- **Guideline for immunogenicity of Mabs**
  - **Conflicting views received; majority are generally supportive.**
  - **Some said the new guideline should be an Annex rather than a guideline by itself but this is not possible in the EMEA framework.**
  - **Some comments contradictory.**
  - **Criticism of 'predictive' section.**
  - **No need to treat biosimilar mAbs differently from innovator mAbs.**

Workshop- Guidelines

There was a closed workshop on the ‘Similar biological medicinal products containing monoclonal antibodies’ and ‘Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use’ guidelines held at EMA on 24th October 2011.

Issues relating to both guidelines were discussed.

Some modifications to guidelines suggested by discussion at workshop.

mAb Immunogenicity Guideline:

- **Variability of immunogenicity of mAbs and its consequences.**

  Title altered and section shortened to avoid overlap with general GL
- **Approaches which may be helpful in predicting unwanted immunogenicity of mAbs – Deleted-covered in general guideline**
- **The clinical consequences of immunogenicity of mAbs**

  Title altered, shortened and combined with risk section
- **Problems experienced with screening and confirmatory assays used in assessing immunogenicity of mAbs – minor changes**
- **Assessing the neutralizing capacity of antibodies induced against mAbs – minor changes.**
- **Risk-based Approach: Title altered, rewritten and combined with clinical section; subheadings changed**

  -Risk of mounting an unwanted immune response

  -The severity of clinical consequences of an immune response

  -Consequences with regard to different risk classes

mAb Immunogenicity Guideline: Revised

Originally - ‘Annex’ not allowed;
Recently, the word ‘Addendum’ allowed so title page has a statement reflecting that this GL is an addendum to general GL and states that it ‘should be read in conjunction’ with it.

Contents of Revised GL:

- Factors which affect the unwanted immunogenicity of mAbs
- Problems experienced with screening and confirmatory assays used in assessing immunogenicity of mAbs
- Assessing the neutralising capacity of antibodies induced against mAbs.
- Clinical aspects of the immunogenicity of mAbs
  - Risk identification
  - Risk assessment

Immunogenicity testing

- Although assay design, strategy & extent of testing are likely to vary between mAbs, certain key elements need to be addressed in designing immunogenicity assays for application during clinical testing -
- Sensitivity - Sufficiently sensitive assays to detect clinically relevant levels of antibodies
- Interference – Assay results should not be confounded by matrix interference or from residual product. Any interference needs to be evaluated and strategies to minimise/overcome this implemented
- Biological/Functional consequences – Since induced antibodies can have multiple biological effects e.g., neutralizing activity etc, assays should be designed to detect these consequences.
- Risk – Does the product pose a high/low risk?

Every mAb needs to be evaluated for immunogenicity individually and appropriate strategies adopted for each mAb development programme

Immunogenicity testing : Some Considerations

- Lack of secondary reagents that discriminate between serum abs & mAb product so this needs to be considered
- Long half-life; often administered chronically at high doses so samples are expected to contain high levels of therapeutic/immune complexes which interfere with detection of induced abs. This needs evaluation and an optimal strategy defined and built in to the assay.

  Although a suitable positive control can be used for evaluation of the strategy adopted, it does not reflect the 'real' situation with clinical samples (varying isotypes, affinities etc within/between patients over time).
- Interference from other substances e.g., soluble target, Fc binding factors/ receptors, disease specific factors e.g., rheumatoid factors (RF) should be evaluated & mitigated as appropriate and built in to the assay
- Pre-existing antibodies – if detected, investigate reactivity and implement strategy; problematical from bioanalytical, efficacy & safety perspective
- Antibody controls - Positive: Human serum (ideal), Polyclonal sera from hyperimmunised animals, affinity purified, mAbs, anti-idiotypic antibodies; Negative: pre-therapy sera, irrelevant antibody, normal donor sera (individual or pooled).

Immunogenicity Testing

- The immunogenicity of mAbs is complex; prediction difficult due to variability of the antibodies and the various factors impacting on immunogenicity & its consequences

- Guideline advocates 'Risk-based approach' for immunogenicity testing. This incorporates both probability and the severity of clinical consequences. Cannot be generalised due to diversity of risk factors and mAbs & mAb -related products
  - Consider factors & discuss individually their relative significance w.r.t the risk
  - Applicants need to define what 'risk' means. This will influence decisions & justification of concept for design & extent of testing.

mAb products should not be viewed as 'low-immunogenicity-risk' class.
Case-by-case risk analysis warranted

Sampling strategy varies & depends on the risk

- For High risk - From early stages, frequent, sequential sampling and testing conducted throughout the whole clinical programme. Analyze samples in real time.
- For Low risk – In late stages of development, reduced sampling possible provided that no adverse events or reduced efficacy is observed. Banking of samples routinely is imperative throughout the whole development programme. Possibility of retrospective analysis

Immunogenicity testing

- Multi-tiered Approach - Valid and sensitive assays which can detect relevant antibodies
  - For example, for heterologous e.g. rodent sequence or human chimaeric mAbs - antibodies induced against various epitopes e.g. anti-Fab, anti-Fc.
  - Humanised or human sequence mAbs - mainly anti-idiotypic & can compromise clinical responses. In some cases, antibodies induced against the constant region of human or humanised mAbs and impact on the immunobiological function
  - mAbs containing non-human carbohydrate structures such as

    gal alpha 1, 3 gal can be problematical because of the presence of pre-existing IgE antibodies against these structures (potential for allergic reactions); patients will need to be tested for pre-existing IgE antibodies prior to treatment. If mAb induces high incidence of allergic reactions on first administration, need to test
  - In certain instances, IgE antibodies may be induced by the product.

Immunogenicity testing

- Evaluation of neutralizing capacity of antibodies is expected; deviations need to be justified
- Mode of action of mAb likely to determine the NAb assay strategy
- Assays –
  - Measured using Bioassays or Competitive ligand binding assays.

    CLBs may be the method of ‘choice’,at least for some mAbs.
  - Due to the multi-faceted mechanism of action for mAbs, tests for both the blocking of binding activity and interference with an immunobiological mode of action need to be considered. In this regard, a cell based assay for measuring NAb has an advantage.

Considerations for assessment of immunogenicity of MAbs

- New guideline & general guideline – need to be considered together when planning immunogenicity studies; strategy for assessment needed

- Guideline does not recommend a particular assay;
  - Evaluation of different platforms prior to final selection of screening assay; >1 assay platform may be needed for screening,
  - generic assay/strategy does not fit all mAbs; case-by-case approach needed
- Justification on the suitability of the chosen approach(es), taking into consideration relative merits & limitations of the methods. Other assays e.g., IgE assay or for assessment of reactivity of pre-existing antibodies

As a starting point, standard aspects of immunogenicity as described in the general guideline should be addressed for every new therapeutic mAb, taking into account its characteristics, the nature of the intended use and the therapeutic indication. Preliminary immunogenicity data can provide information which may be of use for planning later studies. Based on a risk identification and assessment strategy as further described below, the standard immunogenicity testing programme may be reduced with thorough justification, or may need to be intensified, depending on the level of risk identified

Antibodies and Adverse Effects - EPO

>60 PRCA cases identified in Thailand. 14 EPO products marketed. Link to product(s) ?

Safety Study for Binocrit 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

Cause(s) ?

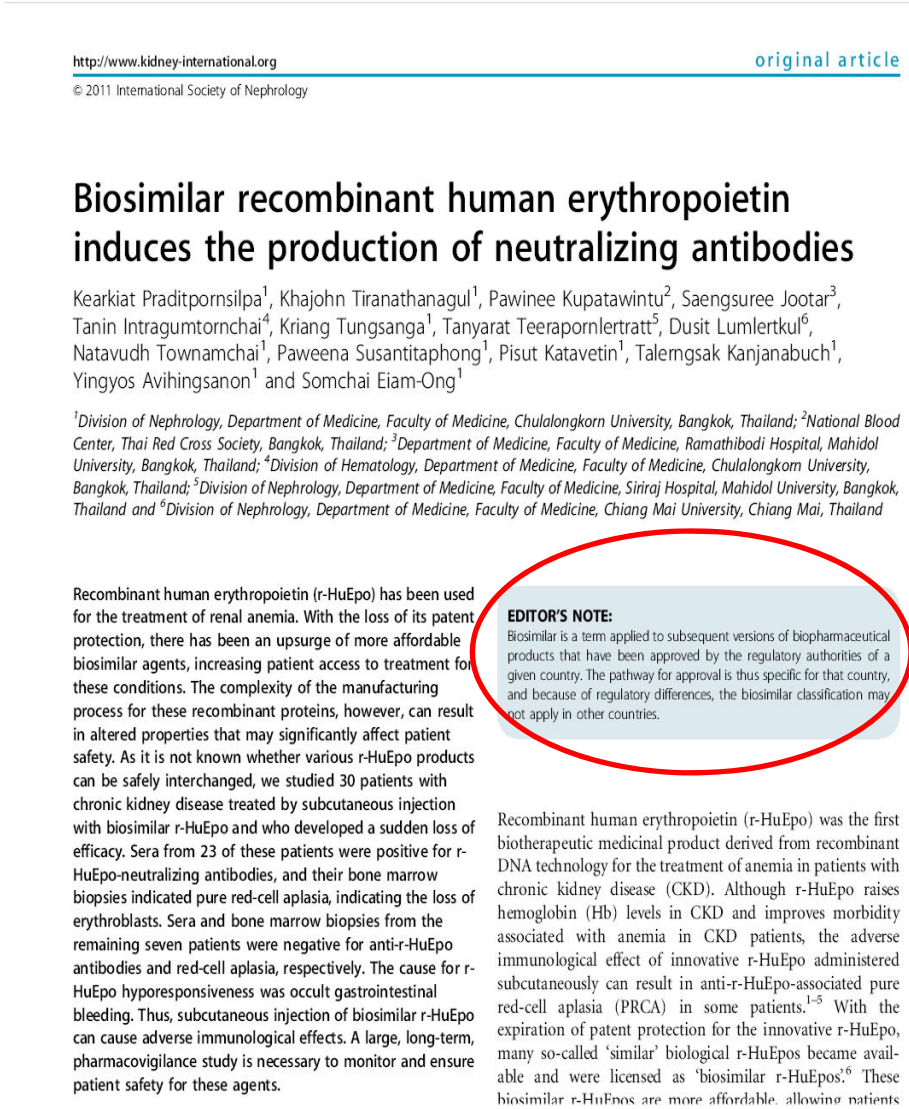
Binocrit approved - 2007
Rigorous physico-chemical, biological characterisation & clinical trial data
Brockmeyer & Seidl (2009) Biologicals

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

- 2002 - 13 cases in CRF patients, rapid development of severe transfusion dependence within months of therapy, resistant to other EPO products.
- Pre 1998 – 2/3 cases
- 1998 to June'05 – 260+cases worldwide

Casadevall et al – NEJM 2002; 346 : 469-475

‘Biosimilar’ EPO is Immunogenic?



http://www.kidney-international.org original article

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Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies

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Recombinant human erythropoietin (r-HuEpo) has been used for the treatment of renal anemia. With the loss of its patent protection, there has been an upsurge of more affordable biosimilar agents, increasing patient access to treatment for these conditions. The complexity of the manufacturing process for these recombinant proteins, however, can result in altered properties that may significantly affect patient safety. As it is not known whether various r-HuEpo products can be safely interchanged, we studied 30 patients with chronic kidney disease treated by subcutaneous injection with biosimilar r-HuEpo and who developed a sudden loss of efficacy. Sera from 23 of these patients were positive for r-HuEpo-neutralizing antibodies, and their bone marrow biopsies indicated pure red-cell aplasia, indicating the loss of erythroblasts. Sera and bone marrow biopsies from the remaining seven patients were negative for anti-r-HuEpo antibodies and red-cell aplasia, respectively. The cause for r-HuEpo hyporesponsiveness was occult gastrointestinal bleeding. Thus, subcutaneous injection of biosimilar r-HuEpo can cause adverse immunological effects. A large, long-term, pharmacovigilance study is necessary to monitor and ensure patient safety for these agents.

EDITOR'S NOTE:
Biosimilar is a term applied to subsequent versions of biopharmaceutical products that have been approved by the regulatory authorities of a given country. The pathway for approval is thus specific for that country, and because of regulatory differences, the biosimilar classification may not apply in other countries.

Recombinant human erythropoietin (r-HuEpo) was the first biotherapeutic medicinal product derived from recombinant DNA technology for the treatment of anemia in patients with chronic kidney disease (CKD). Although r-HuEpo raises hemoglobin (Hb) levels in CKD and improves morbidity associated with anemia in CKD patients, the adverse immunological effect of innovative r-HuEpo administered subcutaneously can result in anti-r-HuEpo-associated pure red-cell aplasia (PRCA) in some patients.[1–5] With the expiration of patent protection for the innovative r-HuEpo, many so-called ‘similar’ biological r-HuEpos became available and were licensed as ‘biosimilar r-HuEpos’.[6] These biosimilar r-HuEpos are more affordable, allowing patients

Under the generic drug paradigm of the Thai Food and Drug Administration, 14 biosimilar r-HuEpos were licensed by 1 January 2009. These products came from various countries such as Argentina, China, South Korea, and India.

The number of cases using biosimilar r-HuEpos have increased enormously because of their more affordable prices. With their usage, adverse effects of the less than identical therapeutic agents have started to increase.

Many clinicians in Thailand were starting to see an increase in PRCA cases which raised an important issue whether the immunogenicity of biosimilar therapeutic agents were indeed equivalent to the innovative r-HuEpo.

Misleading definition

Worldwide consensus - A biosimilar is a biotherapeutic accepted by a regulatory pathway which requires biological and clinical comparison with the original licensed product .

Are all Biosimilars really Biosimilars?

- Terms ‘Biosimilars’, ‘Similar Biological Products’ & ‘Non-Innovator Products’ etc often used interchangeably. Can be incorrect.

- Non-Innovator Products or ‘Me-to’ products usually have not been evaluated using comprehensive comparability studies. They are not biosimilars

- This can be very important from the immunogenicity viewpoint.

Biosimilars-Definition

NATURE BIOTECHNOLOGY | OPINION AND COMMENT | CORRESPONDENCE

Biosimilars—why terminology matters

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To the Editor:

As members of the Biosimilar Medicinal Products Working Party (BMWP) at the European Medicines Agency (EMA; London), we would like to draw readers' attention to problems arising from imprecise usage of the term biosimilar (similar biological medicinal product) in the literature. We have repeatedly noticed misinterpretations of the biosimilar concept as well as inconsistent use of terminology and are concerned about potential implications of this, such as negative perception and impaired acceptance of biosimilars among prescribing physicians and patients. Here we outline the scientific principles underlying the biosimilar concept in the European Union (EU; Brussels). We also address problems in terminology in the context of global emergence of copy biologicals (including 'true' biosimilars) and 'biobetters', and the potential for unjustified concerns about the efficacy and safety of biosimilars in their stricter sense.

Biosimilars-Definition

According to the EU, a biosimilar medicinal product is a copy version of an already authorized biological medicinal product (the reference product) with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise[2, 3]. Biological medicinal products are derived from living cells or organisms and consist of relatively large and highly complex molecular entities that are often difficult to fully characterize by currently available analytical methods. Because of the inherent variability of the biological system used as manufacturing process, the resulting biological product will also display a certain degree of variability ('microheterogeneity').

Biosimilars-Definition

Table 1: Proposal for a more precise terminology.

Term(s)	Definition	Implications
Biosimilar[a]	Copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise.	Only very small differences between biosimilar and reference with reassurance that these are of no clinical relevance. Extrapolation of clinical indications acceptable if scientifically justified.
Me-too biological/biologic Noninnovator biological/biologic	Biological medicinal product developed on its own and not directly compared and analyzed against a licensed reference biological. May or may not have been compared clinically.	Unknown whether and which physicochemical differences exist compared to other biologicals of the same product class. Clinical comparison alone usually not sensitive enough to pick up differences of potential relevance. Therefore, extrapolation of clinical indications problematic.
Second-generation (next-generation) biological/biologic Biobetter	Biological that has been structurally and/or functionally altered to achieve an improved or different clinical performance.	Usually stand-alone developments with a full development program. Clear (and intended) differences in the structure of the active substance, and most probably different clinical behavior due to, for example, different potency or immunogenicity. From a regulatory perspective, a claim for 'better' would have to be substantiated by data showing a clinically relevant advantage over a first- or previous-generation product.

[a]Comparable terms defined by the same/similar scientific principles include the WHO's 'similar biotherapeutic products' and Health Canada's (Toronto) 'subsequent-entry biologicals'.

Tables index

Update on Standardisation

Standardisation Activities:

- Standardisation of a neutralising antibody assay for detection of antibodies against IFN-beta (EMA) – permission to distribute MxA antibodies obtained (MTA – 18th Jan'12); manuscript recently drafted
- IFN-beta antibody reference preparation (pooled human serum) available
- Fabry's antibody standardization initiative – reference standard for anti-alpha galactosidase antibodies – pending legal issues
- Provision of antibody reference panel for standardisation of EPO antibody assays (WHO, Oct 2010)
  - Panel of human antibodies of different characteristics (isotypes, affinities) for use as performance indicators for different EPO antibody assays (MTA – 6th Jan'12)

Legal issues (e.g., MTAs) are major hurdles; time consuming and cause years of endless delay

Standardisation Activities : 2012

- Antibody reference panel for standardisation of EPO antibody assays – WHO ECBS endorsement (Oct'10)
  - Lyophilization & Collaborative study (small)
- 3rd IS for TNF-alpha* (candidate materials/standards in - house) – WHO ECBS for endorsement (Oct'12)
- 1st IS for Soluble TNF receptor II Fc fusion protein* (candidate materials currently being procured) – WHO ECBS for endorsement (Oct'12)
  - Lyophilization & Collaborative studies (Oct'12) – joint study*

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