Safety concerns with early clinical development of biologicals and biosimilars: clinical relevance of anti-drug antibodies

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Topics

- What makes therapeutic proteins different and what are the safety issues
- Immunogenicity and its clinical significance
- Other safety issues of biologics/biosimilars
- The PK studies in volunteers in biosimilar development

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Shifting paradigms: biopharmaceutics versus low molecular weight drugs

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To celebrate and commemorate Prof. Dr. H.E. Junginger's 60th birthday

Abstract

Differences between classical drugs and biopharmaceuticals

- Relative simple
- Species independent
- Non-immunogenic
- Single molecule
- Metabolized
- Short acting
- Frequent dosing
- Toxic

- Specific mechanism
- Linear dose-response
- Oral
- Generic

- Large complex
- Species specific
- Immunogenic
- Heterogeneous
- Degraded
- Long acting
- Intermittent dosing
- Exaggerated pharmacodynamics
- Pleiotropic effects
- Bell shaped dose response
- Parenteral routes
- Biosimilar

Main safety issues of biologics

- Pharmacodynamic effects
- Immunogenicity
- Skin reactions

Immunogenicity of therapeutic proteins as key issue

History of the medical use proteins

- Proteins of animal origin (e.g. equine antisera, porcine/bovine insulin): foreign proteins
- Human derived proteins (e.g.growth hormone, factor VIII): no immune tolerance
- Recombinant human proteins(e.g.insulin, interferons, GM-CSF): ??

Conclusion 1 : Nearly all biopharmaceuticals induce antibodies

Conclusion 2: There are two mechanisms

- Reaction to neo-antigens (foreign proteins)
- Breakdown of immune tolerance

Types of immune reaction against biopharmaceuticals

Breaking of self-tolerance

Type of product	Human homologues
Characteristics of antibody production	Slow, after long treatment, binding antibodies, disappear after treatment
Cause	Mainly impurities and aggregates

Factors influencing immunogenicity

- Main primary factors
  - Level and type of aggregation ("breaking" of tolerance)
  - Level of non-human characteristics (classical immune activation)
- Modulating factors
  - Formulation
  - Route of administration
  - Dose and length of treatment
  - Concomitant therapy
  - Patient characteristics
    - Disease
    - Genetic background
  - Unknown factors

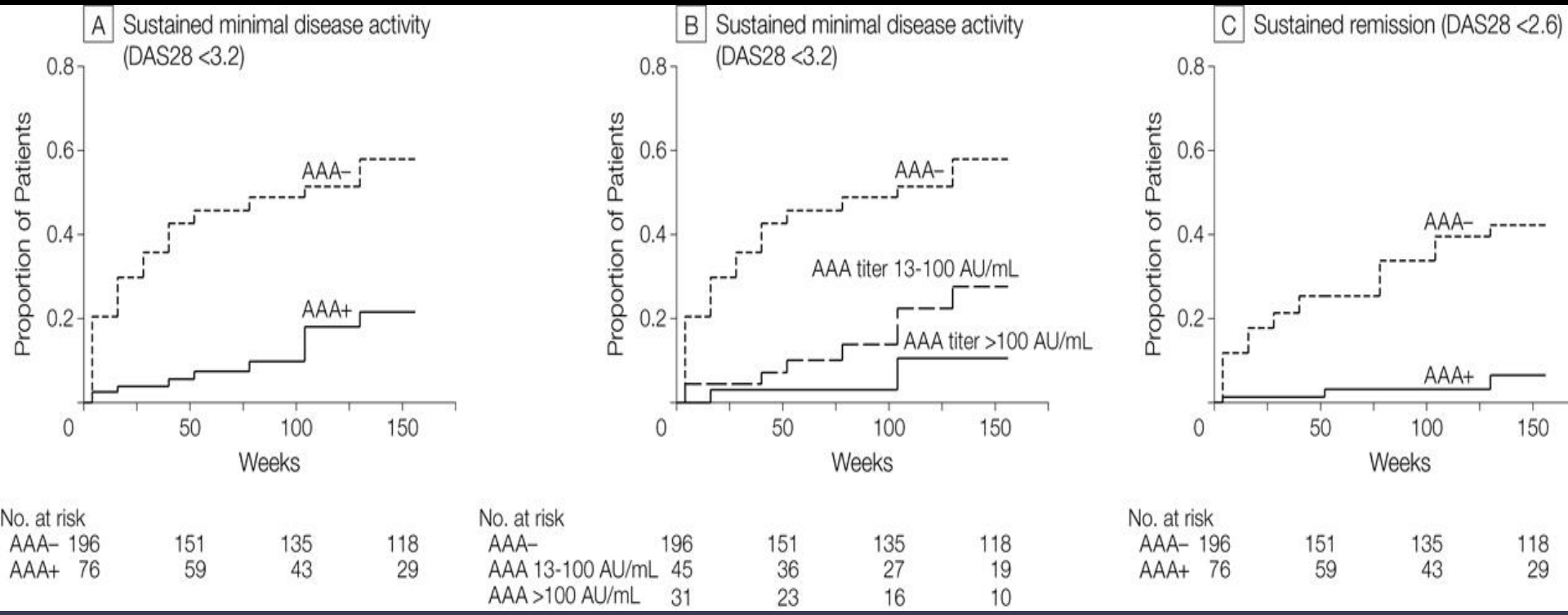
Schellekens H. *Nat Rev Drug Discov* 2002;1:457–462

Year of introduction	Product	Details	Incidence of Immunogenicity[1]	Immunogenicity related adverse effects
1922	Crystallized bovine and porcine insulins from pancreas extraction.		>95% High incidence in almost all patients receiving insulin.	Frequent anaphylaxis, local and system hypersensitivity, insulin resistance
1940ties	NPH (neutral protamine Hagedorn)and lente insulins	Intermediate-acting insulins. Suspension of insulin in combination with protamine (NPH) and zinc	Higher immunogenicity when compared to pure insulins	Comparable to common insulin preparations
1970ties	Purified monocomponent bovine and porcine insulins	Purified by gel filtration chromatography and ion exchange chromatography,	~60% Reduced immunogenicity of monocomponent insulin compared to polycomponent insulin.	Drastic reduction of anaphylaxis, local and system hypersensitivity and skin reactions. Clinical resistance rare.
1980ties	Semisynthetic conversion of porcine insulin		~40%	Rare and comparable with purified monocomponent animal insulins
1980ties	r-DNA derived human insulin		~40%	Rare and comparable with semi-synthetic insulins
1990ties	Insulin analogues		~40%	Rare and comparable with unmodified human insulins

Consequences of antibodies

- Loss of efficacy
  - Interferon alpha 2
  - Interferon beta
  - TNF-inhibitors
  - Algasidase-beta
  - Many others
- Cross neutralization of endogenous factors
  - EPO
  - MGDF
- Anaphylactoid reactions, serum sickness
  - Monoclonal antibodies

Sustained Disease Activity and Remission in Patients Wit and Without Antiadalimumab Antibodies

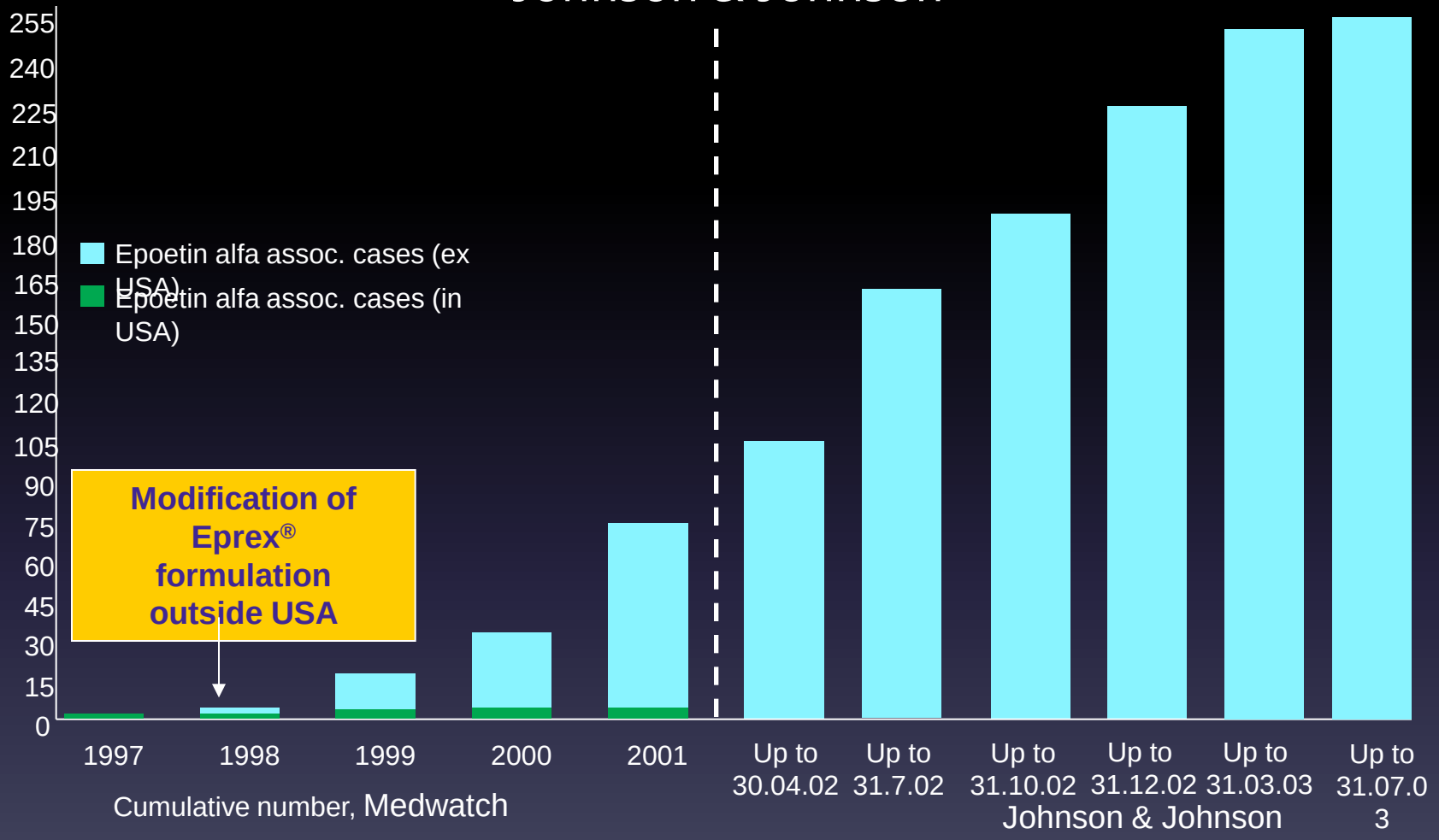


Bartelds, G. M. et al. JAMA 2011;305:1460-1468

Pure red cell aplasia associated with EPO treatment

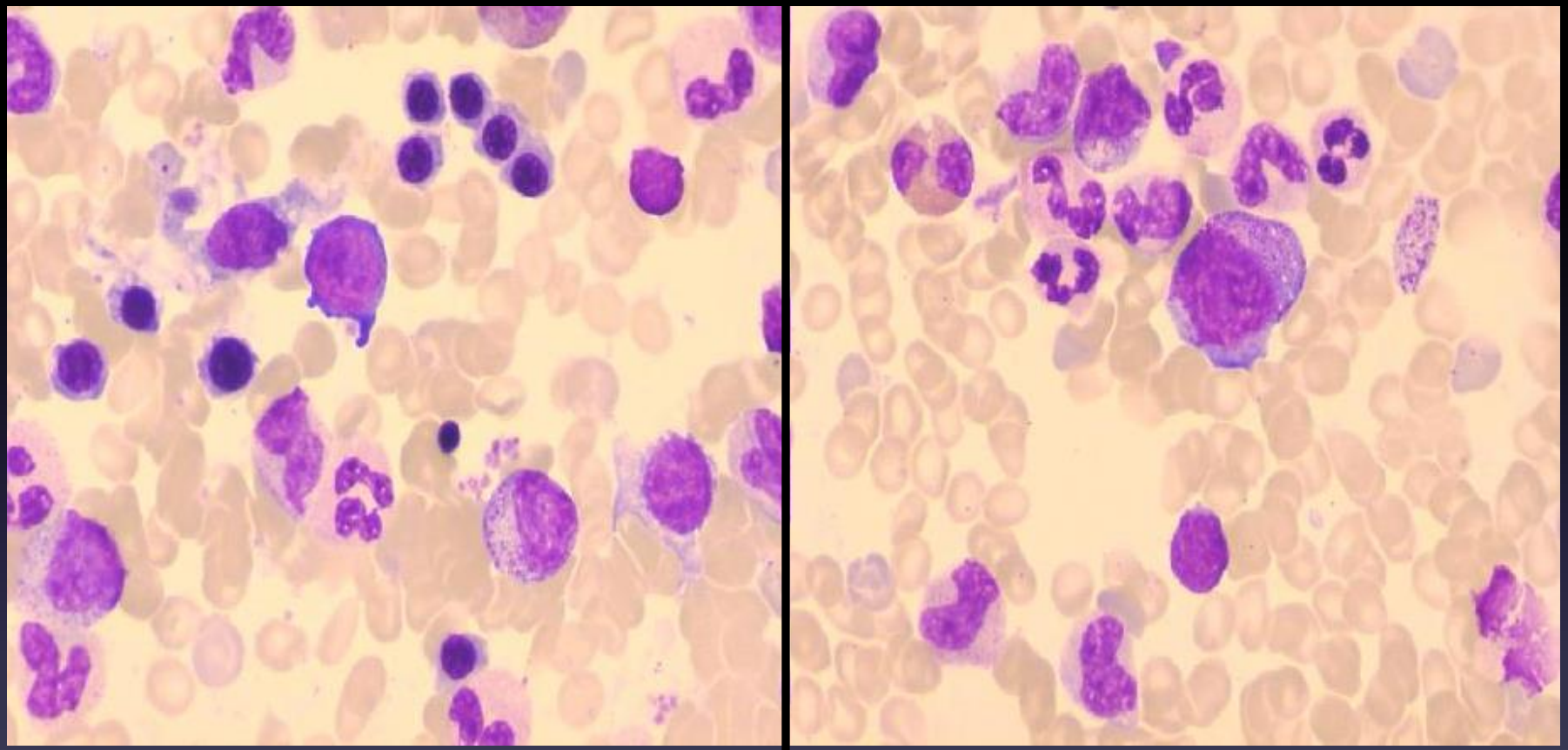
Immunogenicity became an important issue in therapeutic protein development

PRCA cases reported by the FDA and Johnson & Johnson



1. Gershon et al. *N Engl J Med* 2002; 346: 1584–1585. 2. Ortho Biotech. Dear Healthcare Professional letter, 17 July 2002. 3. Johnson & Johnson Statement. 10 Oct 2003.

Bone Marrow Smear



Normal Bone Marrow PRCA Bone Marrow

What caused Eprex associated PRCA?

A case study showing the importance of product formulation

Product formulation

- Recent concern over use of HSA in Eu
  because of potential transmission of
  infectious viruses or BSE prions

- In 1998, HSA was replaced with polysorbate
  80 in prefilled syringes of Eprex® distributed
  ex-US

What caused Eprex associated PRCA ?

- Formation of micelles associated with Epo (Hermeling et al, 2003): unlikely
- Silicon droplets in the prefilled syringes: very unlikely
- Leachates from rubber stoppers: unlikely
- Mishandling: most likely

Arguments in favor of the mishandling/aggregate explanation

- Epidemiological data
  - Relation with self injection
  - Low incidence
- Other immunogenicity problems with epoetins
  - Epo-associated PRCA in Thailand
  - PRCA/NAB associated withTungsten induced aggregation
- Immunogenicity of other products
  - Interferons
  - GM-CSF
  - Insulin

Can you predict immunogenicity?

The question should be can you predict levels of immunogenicity

Prediction of immunogenicity?

- **PHYSICAL CHEMICAL CHARACTERIZATION**
- **EPITOPE ANALYSIS (IN SILICO/IN VITRO)**
- **REACTION WITH PATIENT SERA**
- **ANIMAL EXPERIMENTS**
  - Convential animals (relative immunogenicity?)
  - Non-human primates
  - Immune tolerant transgenic mice

Buttel I.C. and al. Taking immunogenicity assessment of therapeutic proteins to the next level.
Biologicals 39 (2011) 100-109

CAN YOU PREDICT SIMILARITY IN IMMUNOGENICITY BETWEEN BIOSIMILAR AND REFERENCE PRODUCT?

- Intrinsic immunogenicity will not differ
- Difference in immunogenicity will be related to difference in quality
- So similarity in immunogenicity is predictable

Other safety aspects of biologics/biosimilars

- Pharmacodynamic effects, so potency related
- Animal studies not suitable because of species specificity and immunogenicity
- Adverse effects highly predictable, so who needs animal studies

Safety concerns concerning biologics and biosimilars

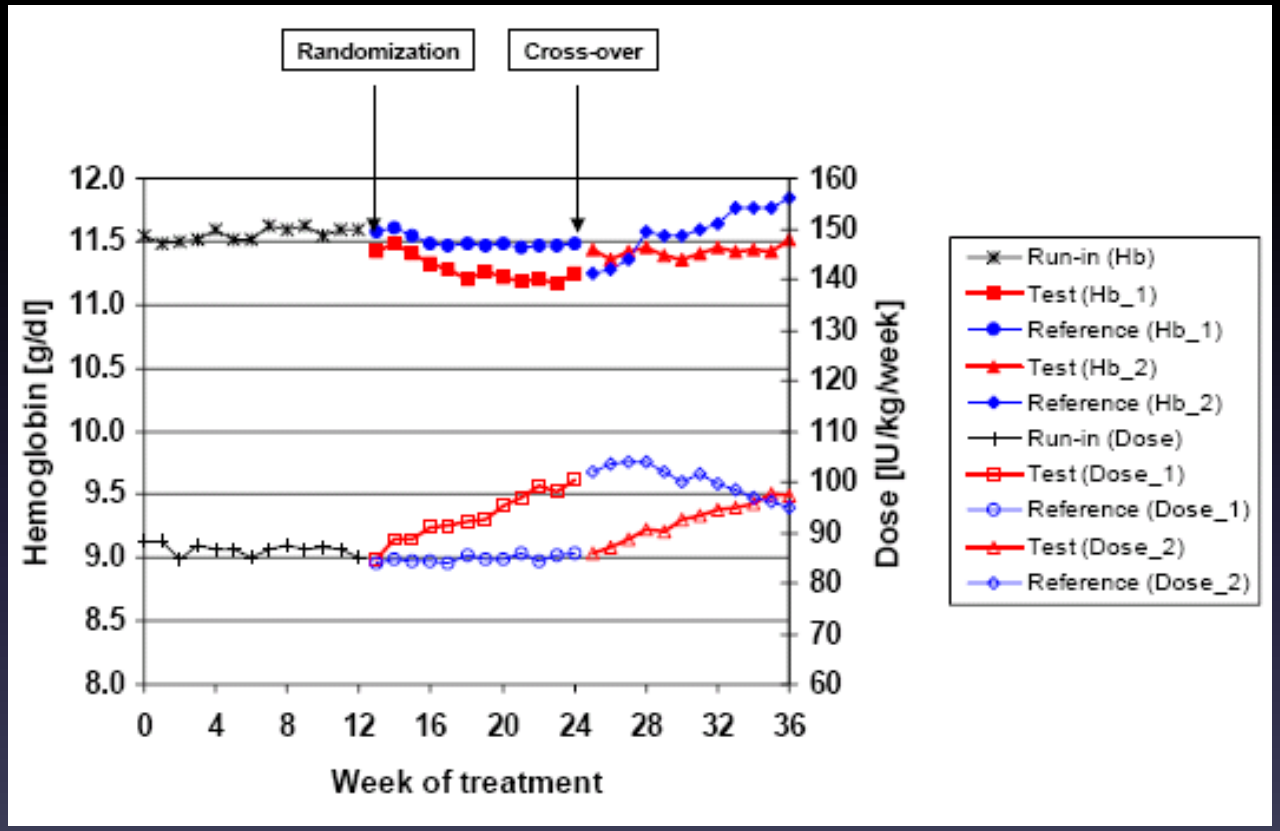
Is there a difference in safety concerns between biologics and biosimilars?

First r-DNA derived human protein drug: human insulin (1982)

Specific safety issues for biosimilars?

- The first generation of original reference products are biosimilars of natural regulating proteins: insulins, interferons, G-CSF, GM-CSF, erythropoetin, etc
- Only one difference seen between a biosimilar and reference product (in potency!)
- No biosimilar specific safety issue identified yet

Haemoglobin levels vs epoetin dose



Retacrit: EPAR - Scientific Discussion. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000872/WC500054374.pdf. Last accessed: January 2014

Potency of different epoetins

	Described Potency (IU/ml)	Measured Potency (IU/ml)
Eprex	10.000	12.884
Binocrit	10.000	11.404
Retacrit	10.000	11.016

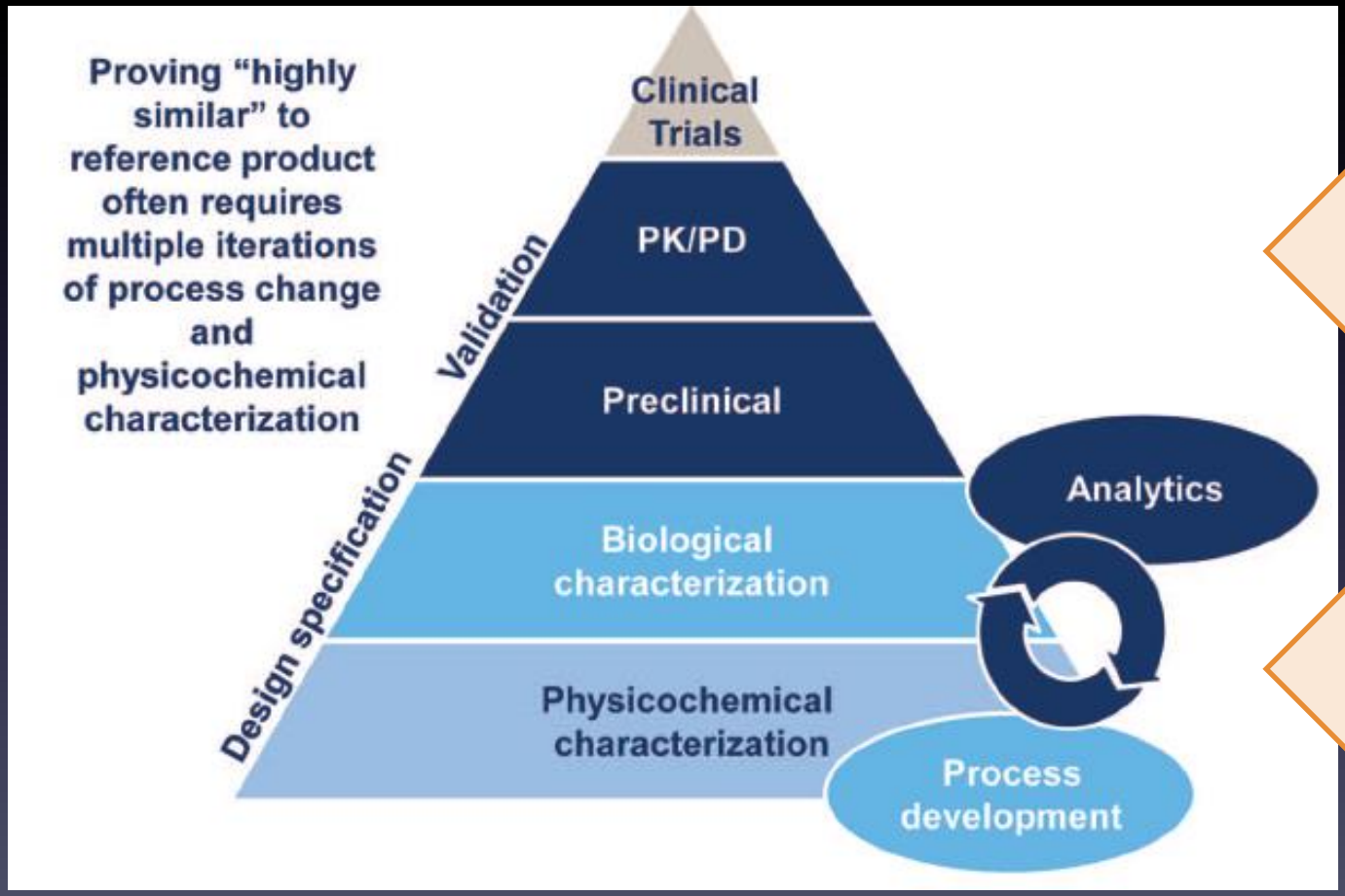
Brinks V, et al. *Pharm Res* 2011;28:386–393

What is needed for a biosimilar

- Candidate should be indistinguisable from the reference product concerning physical chemical characteristics and invitro biological activity
- Potency of the biosimilar should be the same as the original

The use of PK studies in the biosimilar exercise

The current approach for developing a biosimilar



Confirm Biosimilarity

Develop a highly similar product

McCamish. MAbs. 2011;3(2):209-17

Biosimilar terminology

- Totality of evidence
- Different levels of similarity
- Interchangeable and non-interchangeable biosimilars

Aspects of PK studies in biosimilar development

- Do we need them?
- Sensitivity to show differences?
- Dose?
- Redundancy of bridging between US and EU products
- Immunogenicity and paralel design

Changing regulatory environment

- Investors urge big pharma to stop denigrate biosimilars
- Nature Biotech: request for separate INN names for biosimilars is marketing driven
- WHO: affordability as major consideration for new biosimilar regulations
- Colombia: biologics decree allowing the use of published data fo biosimilars
- EMA/CHMP: move to (in vitro) PD markers to show clinical equivalence

Sept 18 2014: President of Colombia singes new Decree for biologics

Different stages of development

- Establishing biosimilarity
  - Reverse engineering
  - Identification
  - Similarity exercise
- Confirming biosimilarity
  - Preclinical stage
  - PK/PD
  - Clinical studies

Based on the principle: level of similarity in physical-chemical and biological characteristics determines the design of the clinical studies .

The first article describing the issues when patents of biologics will expire

Opinion TRENDS in Pharmacological Sciences Vol.23 No.3 March 2002 119

'Biogenerics': the off-patent biotech products

Huub Schellekens and Jean-Charles Ryff

The first patents of biopharmaceuticals derived from recombinant DNA will expire shortly, which raises the possibility of marketing generic products ('biogenerics') with limited documentation, similar to that which occurs with conventional pharmaceuticals. We propose the term off-patent biotechnological products (OPBPs) as an alternative to biogenerics when describing such products. It is questionable whether the majority of OPBPs can be classified as similar to the innovator products, considering the size and complexity of the molecules and the many factors that influence biological activity. There are three classes of OPBPs, each of which needs to meet different regulatory demands when seeking marketing authorization.

study in volunteers that compares pharmacokinetics and/or pharmacodynamics. The question is whether such limited information is sufficient to ensure the efficacy and safety of the majority of biopharmaceuticals that are derived from recombinant DNA.

Biopharmaceuticals

Most biopharmaceuticals are large, complex molecules that, for several reasons, are heterogeneous. Some heterogeneity is caused by the combination of vector and host cell used to produce the biopharmaceutical, and includes clipping (premature termination of translation) and differences in the sites and amount of glycosylation [1,2]. Protein modification might occur during production, depending on the fermentation and cell culture conditions [3]. The extraction and purification procedures can also add to the heterogeneity, as can process-related impurities and the introduction of contaminants that might appear in the final product [4–6]. Lastly, formulation and storage conditions might alter the biological properties and, thus, the response, as a result of physicochemical or physical

Schellekens H and Ryff JC. *Trends Pharmacol Sci* 2002;23:119–121

9:00 AM ET
Aug 11, 2014

BIOTECHS

GENERIC DRUG MAKERS

AMGEN

BIOLOGICS

BIOSIMILARS

FDA

GENENTECH

Big Investors ask Drug Maker Boards not to Denigrate Biosimilars

By Ed Silverman

A group of 19 institutional investors is asking the boards of more than two dozen drug makers and biotechs to agree to various business principles in hopes of supporting use of biosimilar medicines. As you may know, these are designed to emulate brand-name biologics and are forecast to save the U.S. economy valuable health care dollars once they become available.

The investors believe that recent actions taken by some companies could stymie the acceptance of these medicines, which would forestall any projected savings. They also worry that shareholder interests could be harmed if drug makers and biotechs pursue certain policites that are perceived as undermining medical innovation and corporate transparency.

Read More »

Beware of marketing !

EDITORIAL

nature biotechnology

The INN crowd

Moves to give biosimilars nonproprietary names different from brand products are more than a wrangle about words—they could mean biosimilars arrive stillborn to the market.

In recent months, a tussle has emerged between industry trade groups representing brand manufacturers and those representing generics on how biosimilars should be named. Specifically, innovator companies are pressing for the World Health Organization (WHO) to give biosimilars International Nonproprietary Names (INNs) that are different from their brand counterparts. Changing INNs in such a manner goes against several decades of naming convention in the industry, and will likely compromise the ability of biosimilars to succeed in the marketplace.

The WHO established the INN system in 1953 to ensure the "clear

ing the INN due to small differences between an original biologic and that same biologic produced using a slightly different process runs counter to years of naming practice for brand products (a fact that seems to have been conveniently forgotten by innovator companies).

Every now and then, drugmakers of an original biologic make changes to the way they manufacture their product. Such changes can be as trivial as changing their supplier of culture materials or as fundamental as changing the cell line or manufacturing site. When this happens the product may change (a process termed 'drift' in the industry) and regula-

(24-May-2014) Version final adoptada.

Item 9.5 of the agenda

Title: Access to biotherapeutic products including similar biotherapeutic productsand ensuring their quality, safety and efficacy

The Sixty-seventh World Health Assembly,

PP1 Recalling the WHO Constitution, which affirms that the enjoyment of the highest attainable standard of health is one of the fundamental rights of
every human being without distinction of race, religion, political belief, economic or social condition,

PP2 Noting with particular concern that for millions of people, the right to the enjoyment of the highest attainable standard of physical and mental health, including access to medicines, remains a distant goal, that especially for children and those living in poverty, the likelihood of achieving this goal is becoming increasingly remote, that millions of people are driven below the poverty line each year because of catastrophic out-of-pocket payments for health care, and that excessive out-of-pocket payments can discourage the impoverished from seeking or continuing

PP3 Recalling resolution WHA55.14 on ensuring accessibility of essential medicines, which recognizes “the responsibility of Member States to support solid scientific evidence, excluding any biased information or external pressures that may be detrimental to public health”;

The first biosimilar monoclonal antibody in the EU

Extrapolation between different indications completely on in vitro PD data

Remsima EMA Assessment Report. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002576/WC500151486.pdf. Last accessed: January 2014

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 03 June May 2013
2 EMEA/CHMP/BMWP/42832/2005 Rev. 1
3 Committee for Medicinal Products for Human Use (CHMP)

4 Guideline on similar biological medicinal products
5 containing biotechnology-derived proteins as active
6 substance: non-clinical and clinical issues

7 Draft

vitro)
equivalence