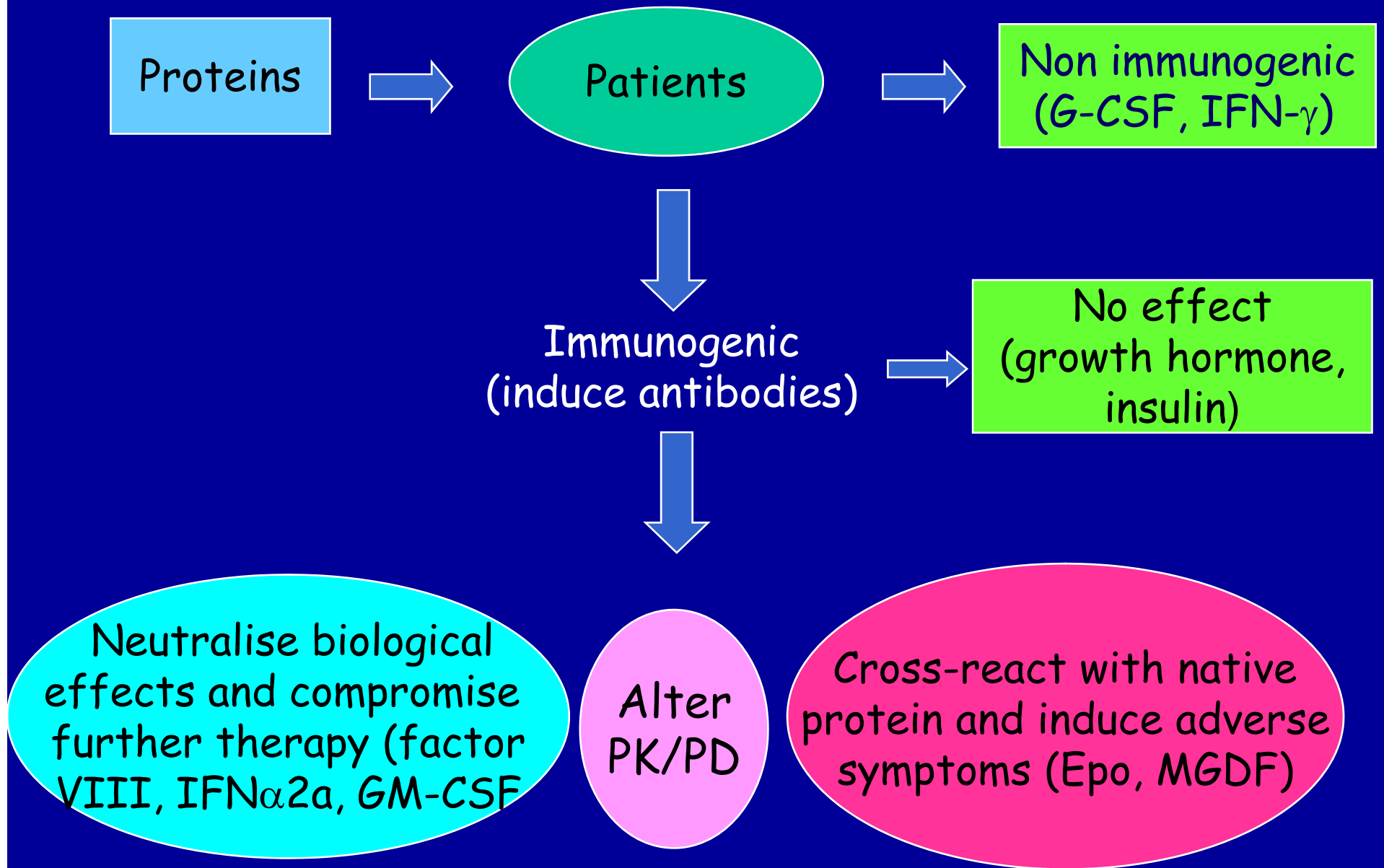


Unwanted Immunogenicity- Issues for Biosimilars

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Unwanted Immunogenicity



Examples - Immunogenic Proteins

Protein Category	Protein	Type & Producer cells	Binding antibodies	Neutralizing antibodies	Clinical consequences
Non human proteins	Calcitonin	Natural	Yes	Yes	Loss of efficacy
	Insulin	Natural	Yes	Yes	Loss of efficacy uncommon
Human proteins	Glucocerebrosidase ¹	Natural	Yes	Yes	Loss of efficacy
	Factor VIII ²	Natural	Yes	Yes	Loss of efficacy
	Follicle stimulating Hormone ³	Natural	No	No	-
Homologous to native proteins	IFN- α 2a	rDNA	Yes	Yes	Loss of efficacy
	GM-CSF	rDNA rDNA	Yes Yes	Yes No	Loss of efficacy No loss of efficacy
	G-CSF	rDNA	No	No	No loss of efficacy
	IFN- β	rDNA	Yes	Yes	Loss of efficacy
	Epo	rDNA	Yes	Yes	Cross reacted with endogenous protein and caused adverse effects.
	IL-2 ⁵	rDNA	Yes	Yes	Loss of efficacy associated with both types of antibodies.
Sequence variants	IFN- β	rDNA	Yes	Yes	Loss of efficacy
	IFN- α Con 1	rDNA	Yes	No	Loss of efficacy not reported
Chemically Modified	Pegylated MGDF	rDNA	Yes	Yes	Cross reacted with endogenous protein and caused adverse effects.
Hybrid molecules	GM-CSF/IL-3 hybrid (PIXY 321)	rDNA	Yes	Yes	Clinical efficacy abrogated
	TNFR2-Ig	rDNA	Yes	No	No correlation with clinical responses or adverse effects.

Examples of therapeutics and their immunogenicity profile

Product name	Protein	Indication	% Patients with immune response
ReFacto	Factor VIII	Hemophilia A	~ 30%
Intron A	Interferon α	Hepatitis C	7%
Roferon A			25%
Pegasys			9%
Pegintron			1%
Betaseron	Interferon β	Multiple Sclerosis	10-45%
Avonex			
Rebif			
Eprex	Erythropoietin	Anemia	Non immunogenic Some cases of pure red cell aplasia with Eprex
Aranesp			
Epogen			
Procrit			
Leukine	Granulocyte macrophage colony stimulating factor	Oncology	2.3% (neutralizing antibodies)
Neupogen	Granulocyte colony stimulating factor	Oncology	Non immunogenic
Neulasta			
Enbrel	TNF receptor II human Ig Fc fusion	Rheumatoid arthritis	16%
Proleukin	Interleukin-2	Oncology	74%

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

Immunogenicity Testing

Testing for antibody responses is essential for ensuring :

- Clinical safety of a biological therapeutic.
- Product Comparability

Immunogenicity Testing - How?

Binding characteristics

- Binding Assays – Immunoassays
- Radioimmunoprecipitation Assays
- Surface Plasmon resonance - Biacore
- Immunoblotting

Neutralising characteristics

- Bioassay

Factors Influencing Immunogenicity of proteins

- Molecular structure - novel epitopes, glycosylation, aggregation, degradation, oxidation, deamidation
- Product impurities
- Formulation
- Dose, route, frequency of administration and duration of therapy
- Immune Status of the Patients, Disease
- Immunomodulatory properties of the protein

Unwanted Immunogenicity

- Biological products can induce antibodies with different characteristics :
 - Non-neutralizing (binding) antibodies against active (& inactive) product related substance(s).
 - Binding antibodies against contaminants.
 - Neutralising antibodies.
 - Mixtures of the above.
 - No Antibodies.
- Different assays are needed for detection and measurement of these antibody types.

Complexity of Proteins

Any subtle change introduced in the manufacturing process of a given product can have enormous implications on immunogenicity

EU Guidelines-Biosimilars

- Similar biological medicinal products (Oct 05)
- Similar biological medicinal products containing biotechnology-derived proteins
 - quality issues (effective - June 06)
 - non-clinical & clinical issues (June 06)
- Biosimilar medicinal products
 - Insulin, GCSF, Somatropin (June 06)
 - EPO (July 06), alpha-IFNs (being drafted).
- Guideline on immunogenicity assessment of therapeutic proteins - currently being re-drafted

Guidance on Similar Biological Medicinal Products containing biotech-derived proteins as active substance: Non-Clinical & Clinical Issues : IMMUNOGENICITY

- In view of the unpredictability of the onset and incidence of immunogenicity, long term results of monitoring of antibodies at predetermined intervals will be required. In case of chronic administration, one-year follow up data will be required pre-licensing.
- The applicant should consider the possibility of antibodies to process related impurities.

Guidance on Similar Biological Medicinal Products containing biotech-derived proteins as active substance: Non-Clinical & Clinical Issues : IMMUNOGENICITY

- If a different immune response to the product is observed as compared to the innovator product, further analyses to characterise the antibodies and their implications to clinical safety, efficacy and pharmacokinetic parameters are required. Special consideration should be given to those products where there is a chance that the immune response could affect the endogenous protein and its unique biological function. Antibody testing should be considered as part of all clinical trial protocols. The applicant should consider the role of immunogenicity in certain events, such as hypersensitivity, infusion reactions, autoimmunity and loss of efficacy.

*Guidance on Similar Biological Medicinal Products containing biotech-derived proteins as active substance: Non-Clinical & Clinical Issues :
IMMUNOGENICITY*

- **There is considerable interindividual variability in antibody response in terms of different antibody classes, affinities, and specificities Thus, data should be collected from a sufficient number of patients to characterise the variability in antibody response.**

EPO GUIDANCE – IMMUNOGENICITY ASPECTS

- **4.3 Clinical safety**
- **Comparative safety data from the efficacy trials are sufficient to provide an adequate pre-marketing safety database.**
- **The applicant should provide at least 12-month comparative immunogenicity data pre-authorization. Retention samples for both correction phase and maintenance phase studies are recommended. For detection of anti-epoetin antibodies, a validated, highly sensitive assay should be used.**

G-CSF GUIDANCE – IMMUNOGENICITY ASPECTS

- **4.2 Clinical safety**
- **Safety data should be collected from a cohort of patients after repeated dosing preferably in a comparative clinical trial. The total exposure should correspond to the exposure of a conventional chemotherapeutic treatment course with several cycles. The total follow up of patients should be at least 6 months.** The number of patients should be sufficient for the evaluation of the adverse effect profile, including bone pain and laboratory abnormalities. **Immunogenicity data should be collected according to the principles described in the “Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues”**

Guidance on Similar Biological Medicinal Products containing biotech-derived proteins as active substance: Non-Clinical & Clinical Issues

IMMUNOGENICITY

- **The assessment of immunogenicity requires an optimal antibody testing strategy, characterisation of the observed immune response, as well as evaluation of the correlation between antibodies and pharmacokinetics or pharmacodynamics, relevant for clinical safety and efficacy in all aspects. It is important to consider the risk of immunogenicity in different therapeutic indications separately.**

Guideline on Immunogenicity Assessment of biotechnology-derived therapeutic proteins

EMA/CHMP/BMWP/14327/2006

- **COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)**
- **GUIDELINE ON IMMUNOGENICITY ASSESSMENT OF BIOTECHNOLOGY-DERIVED THERAPEUTIC PROTEINS**
- **DRAFT AGREED BY BMWP -July 2006**
- **ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION - 25 January 2007**
- **END OF CONSULTATION (DEADLINE FOR COMMENTS)-31 July 2007**
- **REVISION OF DRAFT**

Guideline on Immunogenicity Assessment

- Introduction
- Scope
- Legal Basis
- Risk factors for developing an immune response –
 - Patient and disease related,
 - Product related
- Predictivity of non-clinical models
- Development of assays for humoral and cellular immune response
 - Assay strategy
 - Types of antibody assays
 - Screening assays,
 - Assays for dissecting the specificity and confirming the presence of antibodies
 - Neutralization assays
 - Assay validation
 - Standardisation and reference materials
 - Characterization of antibodies to a therapeutic protein
 - Antibody Characteristics
 - Immunogenicity Assessment strategy –design and interpretation
- Potential clinical consequences of immunogenicity
 - Consequences on Efficacy
 - Consequences on Safety
 - Acute consequences
 - Non-acute consequences
- Clinical Safety
 - Rationale for sampling schedule and kinetics of the antibody response
 - Impact on pharmacokinetics of the product
 - Methodology aspects to assess comparability of immunogenicity potential
- Recommendations for routine monitoring of changes in clinical response and linking immunological findings to clinical events
- Immunogenicity in paediatric indications
- Risk management Plan
- ANNEX - Further details on methods for assessment and characterisation of immunogenicity

Comparative Immunogenicity

- Compares immunogenicity of products ;
Studies need to be designed to demonstrate whether the immunogenicity of the products is the same or significantly different.
- This may affect the design of the studies & their interpretation.
- The consequences of immunogenicity also must be compared.

Comparability

Extrapolation of published data generated using a particular product to another can be misleading and invalid.

Comparability

Conclusions on immunogenicity of products obtained by **comparing data** from **different studies** using different products are usually **invalid**.

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**

Immunogenicity Testing

- Monitoring for antibodies - how long for?
Product related, dependent on schedule,
nature of disease etc.
- assessment of sequential samples usually
needs to be considered.
- post-marketing surveillance too !