Immunogenicity considerations in review and approval of therapeutic proteins

GBC 2017

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An agency of the European Union

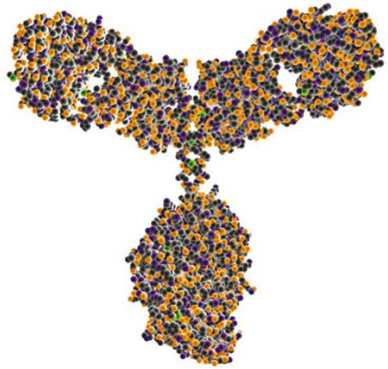
Immunogenicity to therapeutic proteins

Biologicals have complex structures that are recognised by the human immune system, often followed by an immune response

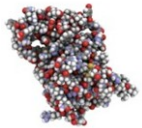
It is not possible to predict

- the incidence of unwanted immunogenicity
- the characteristics of the immune response
- the clinical consequences and significance of such immunogenicity

→ Immunogenicity data needs to be provided in the Marketing Authorisation Application



Monoclonal Ab

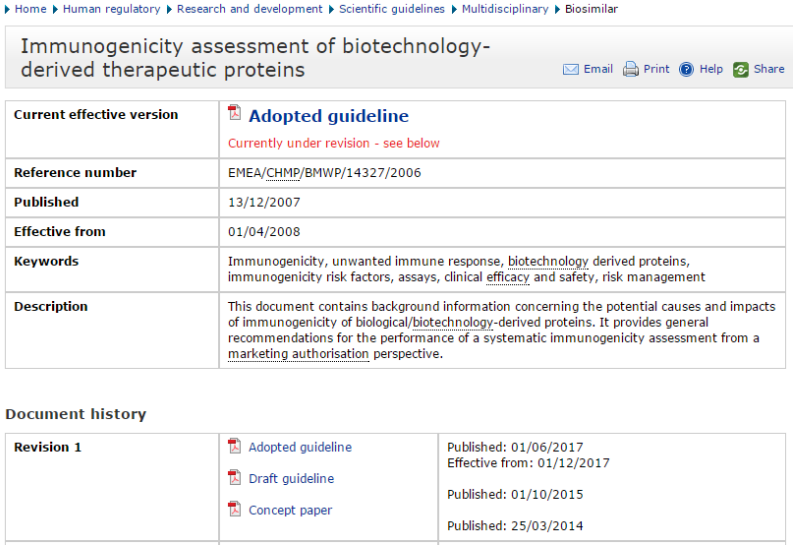


Growth hormone

insulin

Immunogenicity assessment of therapeutic proteins

EMEA/CHMP/BMWP/14327/2006 Rev. 1



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Immunogenicity assessment of biotechnology-derived therapeutic proteins

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Current effective version	**Adopted guideline** Currently under revision - see below
Reference number	EMEA/CHMP/BMWP/14327/2006
Published	13/12/2007
Effective from	01/04/2008
Keywords	Immunogenicity, unwanted immune response, biotechnology derived proteins, immunogenicity risk factors, assays, clinical efficacy and safety, risk management
Description	This document contains background information concerning the potential causes and impacts of immunogenicity of biological/biotechnology-derived proteins. It provides general recommendations for the performance of a systematic immunogenicity assessment from a marketing authorisation perspective.

Document history

Revision 1	Adopted guideline	Published: 01/06/2017 Effective from: 01/12/2017
	Draft guideline	Published: 01/10/2015
	Concept paper	Published: 25/03/2014

- Workshop in March 2016 to discuss comments with stakeholders

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001391.jsp&mid=WC0b01ac058002958c

Revision of guideline – concept paper

- ✓ Requirements of data on antibody assays
- ✓ Role of non-clinical studies
- ✓ Clinical data to study the correlations of anti-drug antibodies to clinical symptoms and signs
- ✓ Risk-based approach to immunogenicity
- ✓ Comparative immunogenicity studies
- ✓ Post-licensing immunological studies
- ✓ Specific guidance for the presentation of immunogenicity data

Guideline contents

- Factors that may influence the development of an immune response against a therapeutic protein (chapter 4)
- Potential clinical consequences of immunogenicity (chapter 5)
- Non-clinical assessment of immunogenicity and its consequences (chapter 6)
- Development of assays for detecting and measuring immune responses in humans (chapter 7)
- Immunogenicity and clinical development (chapter 8)
- Pharmacovigilance (chapter 9)
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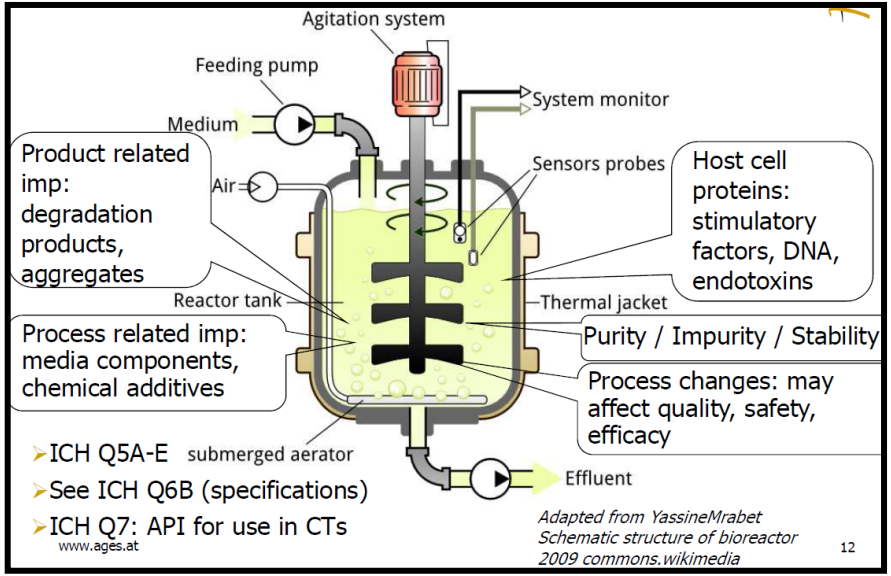
Patient- and disease-related factors

- Genetic factors
- Age-related factors
- Disease-related factors
- Concomitant treatment
- Treatment-related factors
- Pre-existing antibodies

Product-related factors

- Protein structure and post-translational modifications
- Impurities
- Aggregation
- Formulation and packaging



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Consequences of an immune reaction

Purpose of investigating immunogenicity: understand clinical consequences

Efficacy

- Anti-drug-antibodies (ADAs) may inhibit binding on the therapeutic protein to relevant receptors (neutralising antibodies)
- ADAs may increase clearance (clearing antibodies) or decrease clearance (sustaining antibodies)
- Effect may vary from zero to complete loss of efficacy

Safety

- Acute immunological adverse events (infusion-related, anaphylactic/anaphylactoid)
- Delayed hypersensitivity reactions (T-cell mediated and immune complex mediated reactions)
- Autoimmunity (crossreactivity with an endogenous protein)

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Non-clinical aspects

- Proteins are species-specific

Non-clinical studies to predict immunogenicity are not normally required for regulatory purposes

- *In vivo* studies may be helpful in understanding the consequences of immunogenicity in case of cross-reactivity with endogenous proteins
- Use of novel *in vitro* and *in vivo assays/models* encouraged for early development decisions
- Anti-drug antibody measurements may be needed for interpretation of repeated dose toxicity studies

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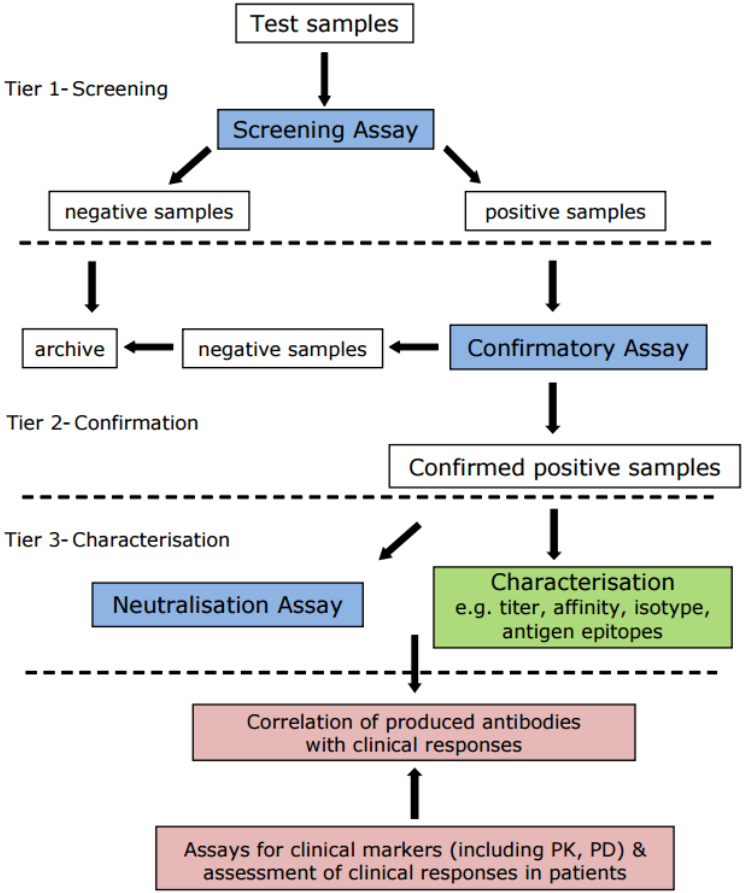
Development of assays

- ✓ Strategy and Antibody Assays
- ✓ Assay Controls and Reagents
- ✓ Assay validation and interpretation of results
- ✓ Assays for comparative immunogenicity
- ✓ Immunogenicity assessment of conjugated proteins and fusion proteins
- ✓ Characterization of antibodies to a therapeutic protein

Analysis strategy (Annex 1)



Screening assays

- Several platforms available, based on detection of antigen-antibody binding
  - Relative merits and weaknesses need to be considered
  - Annex 1: pros and cons of commonly used assays
- False positive rate preferably not exceeding 5%
- False negative results unacceptable
- Consider drug tolerance: the tolerance of the assay to the therapeutic needs to exceed the levels of the therapeutic protein in the samples for ADA testing.

Type of Assay	Advantages	Disadvantages
Direct/Indirect ELISA	High through-put, Inexpensive Easy to use and automate High therapeutic tolerance in solution-phase Generic reagents and instrument	May bind non-specifically Potential for high background Antigen immobilisation may alter antigen conformation and mask epitopes May fail to detect low-affinity antibodies Low therapeutic tolerance in solid-phase Requires species specific secondary reagent
Bridging ELISA	High through-put, Inexpensive Easy to use and automate Low background High specificity (dual-arm binding) Can be used cross-species Generic reagents and instrument	Antigen labeling may alter antigen May fail to detect low-affinity antibodies. Highly susceptible to interference by therapeutic, serum components e.g., anti-human Ig molecules, multivalent targets May not detect IgG4 and IgM
Electrochemiluminescence (with direct/indirect bridging format)	High through-put Large dynamic range Minimally affected by matrix High tolerance to therapeutic Detection signal consistent during life of TAG conjugate	May require two antigen conjugates (indirect) Antigen labeling may alter antigen Susceptible to interference by therapeutic, serum components e.g., anti-human Ig molecules, multivalent targets May not detect IgG4 Vendor-specific equipment & reagents
Radioimmunoprecipitation Assay	Moderate through-put High sensitivity Can be specific Inexpensive	Can be isotype specific May not detect low-affinity antibodies. Requires radiolabelled antigen. Decay of radio-label may affect antigen stability.
Surface Plasmon Resonance	Moderate through-put Determines specificity, isotype, relative binding affinity Enables detection of both 'low-affinity' and high affinity antibodies High tolerance to therapeutic Detection reagent not required	Antigen immobilisation may alter therapeutic Regeneration step may degrade antigen. Sensitivity may be less than binding assay. Expensive. Vendor-specific equipment& reagents

Neutralization assays

- Determination of the neutralizing potential is essential - deviation needs a strong justification
- For a majority of products: two types of assays, cell-based (bioassay) and non-cell-based (competitive ligand binding)
- Mode of action of the therapeutic is critical for selecting a suitable assay format
  - non-cell-based assay relevant for product acting by direct binding to target (e.g. etanercept)
  - cell-based assays recommended for MAb product where effector functions important for clinical effect

Immunogenicity testing – key elements

Sensitivity

Sufficiently sensitive assays to detect clinically relevant levels of antibodies.

Interference

Assay results should not be confounded by matrix/target interference or from residual therapeutic. Interference needs to be evaluated and strategies to minimise/overcome this implemented & justified.

Biological/Functional consequences

Induced antibodies can have multiple biological effects. Assays should be designed to detect them.

Assay Controls and Validation

- Appropriate positive and negative controls essential for data interpretation
- Assays should be properly validated using the same matrix as the samples to be analysed
- Clear criteria for deciding if sample is positive or negative, and how positive results will be confirmed
- Screening for pre-existing antibodies is necessary to ensure that post-treatment data can be interpreted correctly in terms of emergent antibodies

Assays for comparative immunogenicity

- Biosimilars benefit from experience with reference product: lower risk compared to a new product
- However: impossible to predict increase or decrease in immunogenicity → comparative immunogenicity needs to be demonstrated pre-approval
- Head to head studies in sensitive and clinically relevant patient population
- Two options available:
  - Two-antigen assay approach. Both biosimilar and reference product used as antigen. Reflects true immunogenicity of each product.
  - Single assay approach. Biosimilar used as antigen. May underestimate immunogenicity of reference product.

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Immunogenicity and Clinical Development

Sampling schedule

- Sampling for ADA-assessment should be included in the pivotal PK-, PD-, safety and efficacy studies
- Consider PK and drug tolerance of ADA assay
- Allow distinction between transient positive and persistent antibody response
- Duration of follow up: normally one year for continuous chronic treatment

Pharmacokinetics

- PK may be an early indicator of immunogenicity: concomitant sampling encouraged

Immunogenicity and Clinical Development

Impact of immunogenicity on safety and efficacy

- Risk-based approach (consider e.g. previous experience of product/class, presence of potentially immunogenic structures, patient population)

Comparability studies (manufacturing changes & biosimilars)

- Study population needs to be sensitive for differences in immunogenicity and its consequences
- Differences in ADAs warrants further investigations

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Pharmacovigilance

- Immunogenicity may be a potential risk in the Risk Management Plan
- Collection of additional data
  - Extensions of clinical trials
  - Post-approval safety study (PASS)
  - Registries
- Traceability: brand name and batch number should be included in ADR reporting for all biologicals
- Consider changes to the manufacturing process

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Summary of the immunogenicity program

- Planning and evaluation of immunogenicity studies are multidisciplinary exercises
- Relevant data often scattered around the dossier, making assessment challenging

→ Guideline recommend to include a **summary of immunogenicity**

(In 2.7.2.4 Special Studies or, if more detailed, in chapter 5.3.5.3 of the CTD)

Summary of the immunogenicity program

- Analysis of risk factors
- The risk-based immunogenicity program
  - Assay strategy
  - Approach to immunogenicity in clinical trials
  - Impact of the risk assessment on the immunogenicity program
- Immunogenicity results
- Conclusions on the risk(s) of immunogenicity
  - Impact of the immunogenicity on the benefit/risk
  - Tools to manage the risk
  - How to link adverse events to immunogenicity post-marketing

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Any questions?

Further information

[Insert relevant information sources or contact details as applicable.]

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