



Update on the new immunogenicity guideline in the EU

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Disclaimer

- The views and opinions expressed in this review are based on the experience of the presenter and represents the personal views of VS and should not be attributed to any regulatory authority.

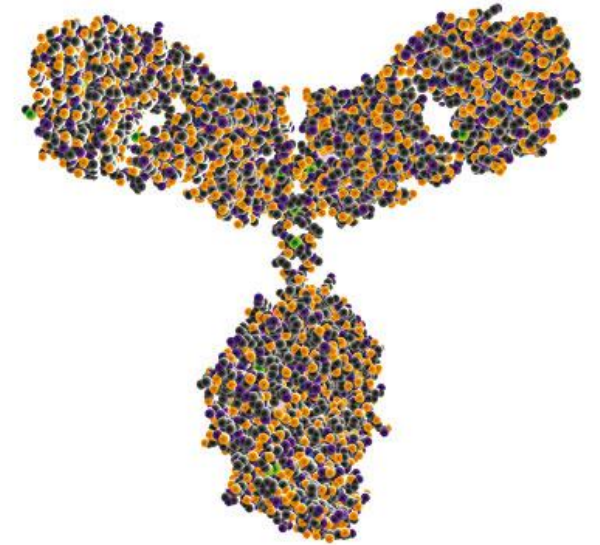


Unwanted immunogenicity- The most challenging issues

- **It is impossible to predict**
 - the incidence of unwanted immunogenicity
 - the characteristics of the immune response
 - the clinical consequences and significance of such immunogenicity
- **THE ABOVE NEED TO BE ASSESSED IN APPROPRIATE STUDIES**

Immunogenicity to therapeutic proteins

- Biologics have complex structures that are recognised by the human immune system
- Even when a monoclonal antibody (MoAb) has been fully humanised (all cDNA derived from humans) it may trigger an immune response
- Immune reactions may result in additional complexities in the use of biological products
- The relationship between dose, exposure, efficacy, as well as toxicity of these molecules
- A regulatory requirement for licensing applications of biologics

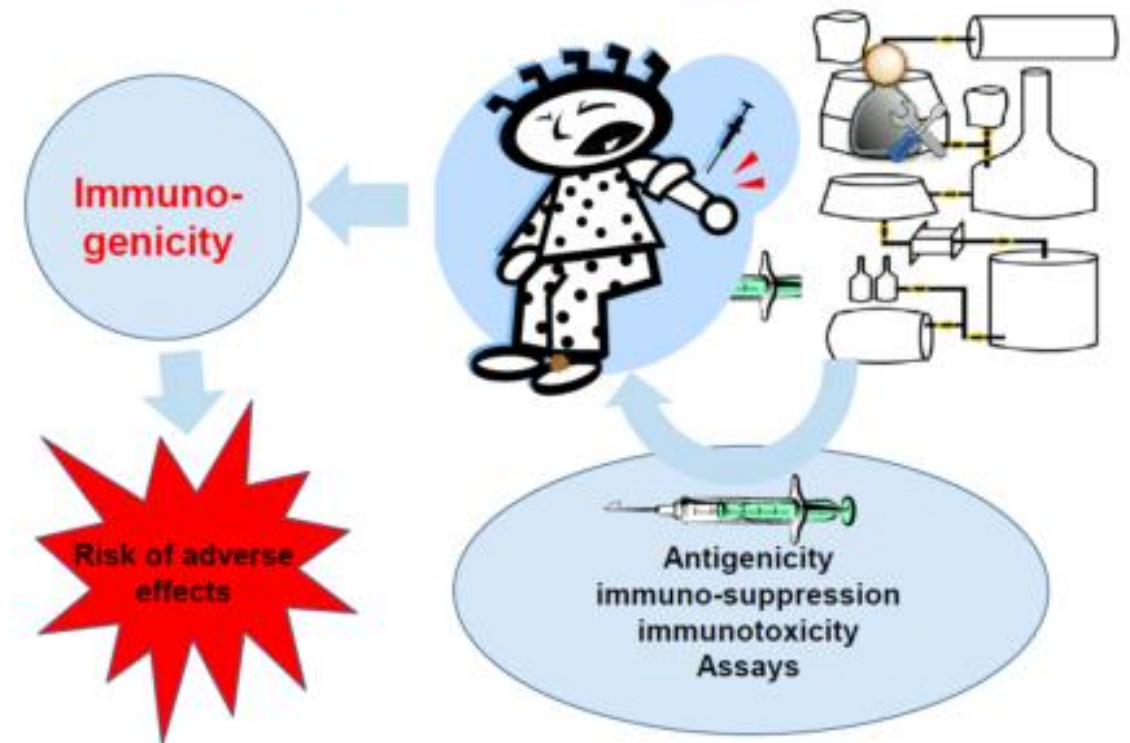




Consequences of an immune reaction

- Administration of therapeutic proteins can induce anti-drug-antibodies - ADAs
 - Transient ADAs
 - Sustained ADAs
- High affinity ADAs produced in "high" amounts
- Affect PK-PD-efficacy and safety
 - Establish a systematic strategy and well-defined criteria for measuring ADAs

A proactive approach





Factors that may influence the development of an immune response

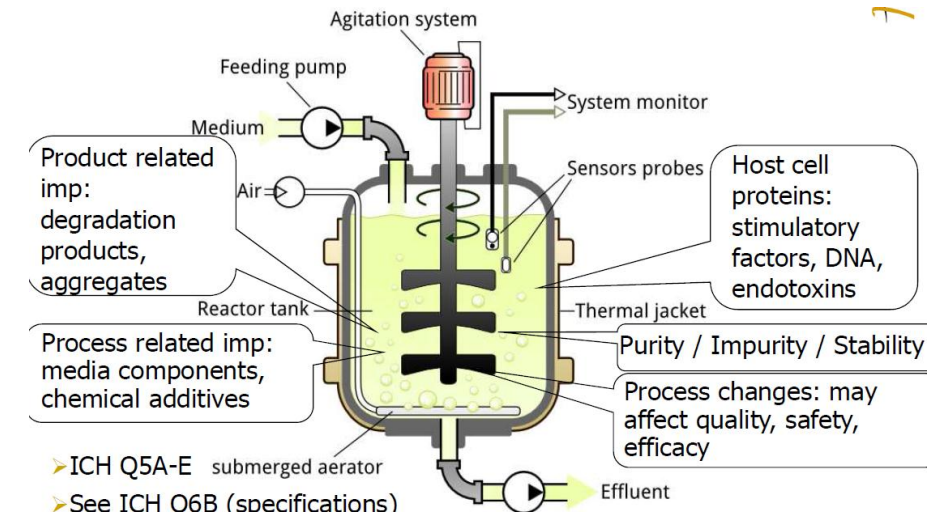
- **Patient- and disease-related factors**

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



- **Product-related factors**

- **Protein structure and post-translational mod.**
- Impurities
- **Aggregation**
- Formulation and packaging



Adapted from YassineMrabet
Schematic structure of bioreactor
2009 commons.wikimedia

Conclusions on immunogenicity



- Immunogenicity issues occur all along the life cycle of a product and particularly when
 - A new therapeutic protein is developed
 - A change is introduced, e.g. manufacturing, formulation, storage conditions
 - A biosimilar is proposed
- Assessment requires
 - an optimal antibody testing strategy
 - validated methodologies and reference standards



European guidance for immunogenicity of therapeutic proteins¹



- Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMA/CHMP/BMWP/14327/2006) (2008)

→ **revision ongoing**

- Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. (EMA/CHMP/BMWP/86289/2010) (2012)
- Biosimilar guidelines
- Guidelines for coagulation factors
- Scientific advice

¹http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&mid=WC0b01ac05800240cb



Concept paper

Concept paper on the revision of the guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMA/275542/2013)

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





Scope of the new guideline

- Guide to a systematic evaluation of the development of an unwanted immune response to a therapeutic protein
 - The guideline applies to proteins , peptides, derivatives (fusion proteins, conjugates)
 - Focus on biotechnology-derived proteins - therapeutic proteins
 - Coagulation factors are excluded



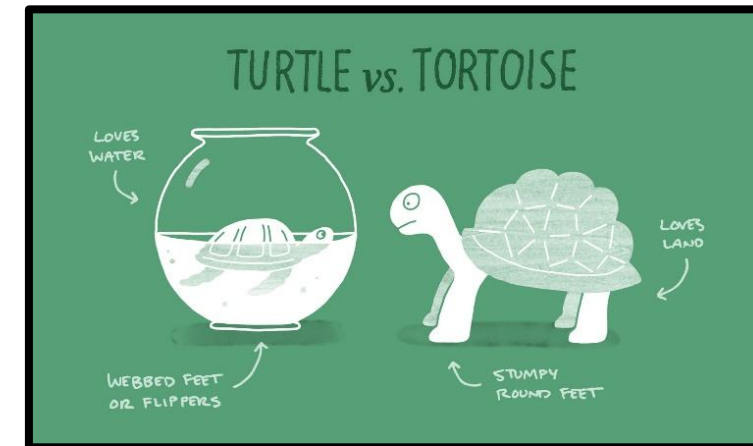
Purpose of the Guideline

- Harmonisation of assessment
 - Common standards throughout Europe
 - Education of assessors
- Regulatory requirements for marketing authorisation
 - General principles
 - What regulators need to know
 - Presentation of the data
- Promotion of a multidisciplinary approach



Revised Guideline: Differences from original

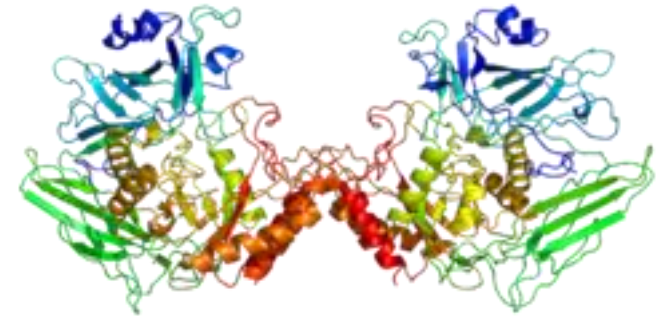
- Condensed; much 'general' and background information removed/shortened
- Brought in line with the MoAb immunogenicity guideline
- Includes risk-based approach
- Takes account of experience gained with assessing immunogenicity of biotherapeutics over the past 10 years
- Contains a request for an integrated summary of immunogenicity





Essentials from the new guideline

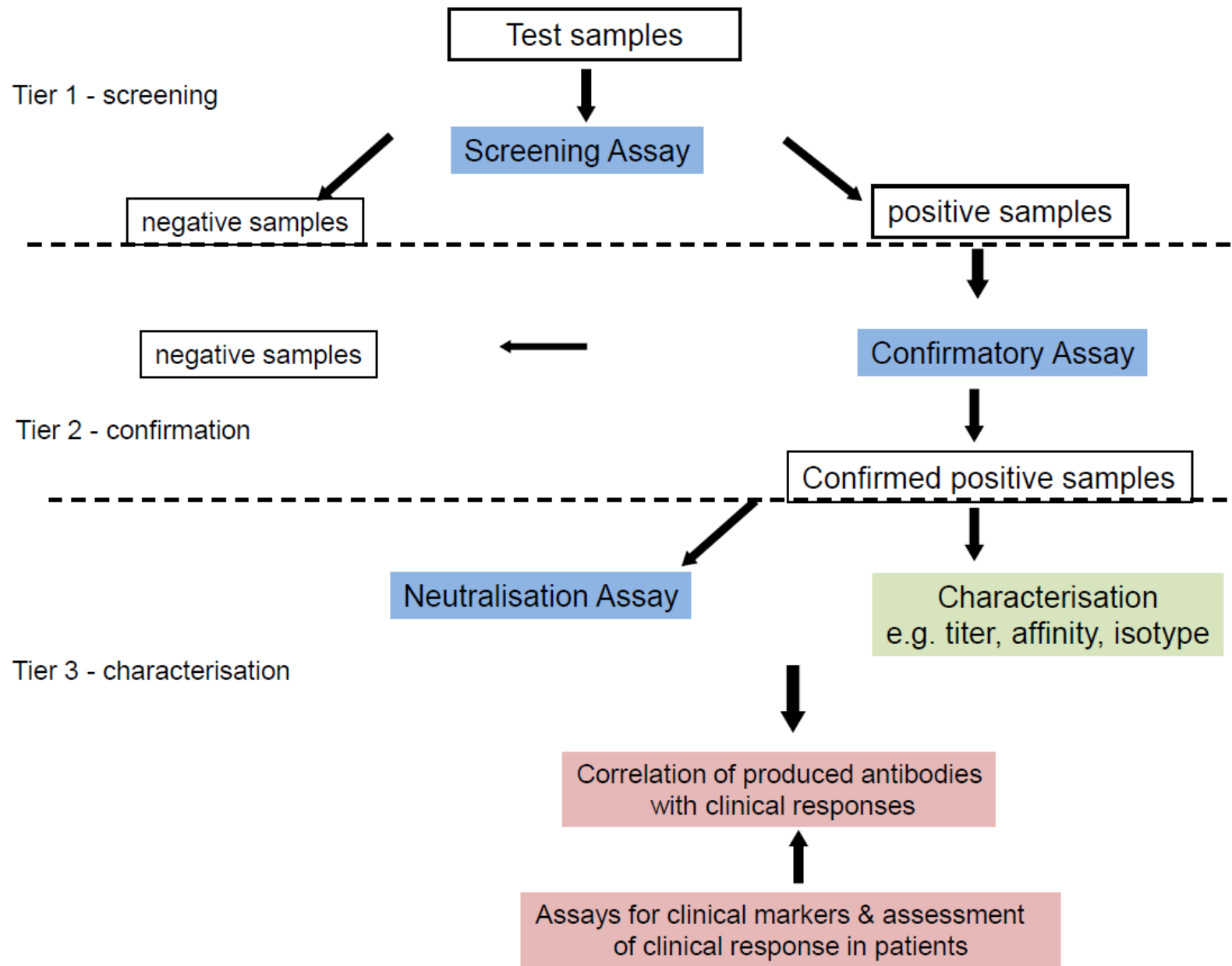
- **Multidisciplinary** summary of immunogenicity
- **Risk assessment**
 - Justification of a risk based approach to immunogenicity
- **From a regulatory point of view; the predictive value of in vivo animal studies is low**
- **Assays**
 - The basis is the development of adequate screening and confirmatory assays
 - properly validated assays
 - **Clinical correlation**
 - integrated analysis of immunological, PK, PD, clinical efficacy and safety data
 - clinical consequences





Strategy and Antibody Assays

- A multi-tiered approach:
 - Screening assay for identification of antibody positive samples/patients
 - Confirmatory assay for minimising false positive results following the initial screen
 - Usually by addition of excess therapeutic and comparing spiked vs unspiked sample - reduction of positive signal for true positives
 - Assay for the assessment of the neutralising capacity of antibodies
 - Assays for measuring the level of the product and for assessing clinical relevance to products
 - assays for relevant biomarkers or PK
 - In some cases, cross-reactivity studies with other products based on the same protein



Data on antibody assays- requirements

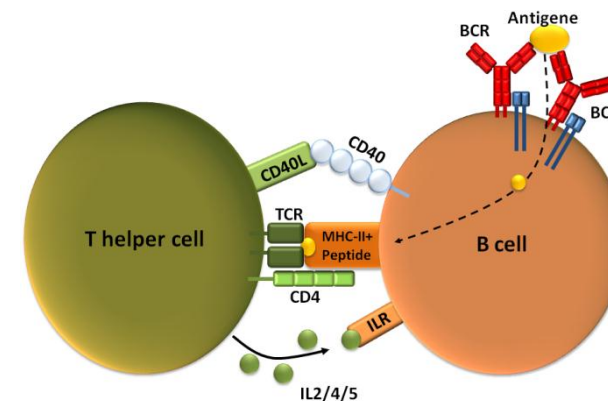
issues to be considered

- No ADAs **→** no immunogenicity: true or not?
 - tolerance, pharmacological effect of the product or immunosuppression (concomitant medication)
 - The applicant has to show that the tolerance of the ADA assay to the therapeutic drug exceeds the levels of the therapeutic in the samples for ADA testing

- Neutralising antibodies (when not necessary, alternative ways, PK/PD)

When to do additional testing?

- Ig isotyping?
- Epitopes, antigenic domains?
- T-cell responses?



- Impact of antibody formation on clinical outcome is important



Mitigation strategies

- Planning a proper immunogenicity program tailored to the substance in question
- **The section 10, Summary of the immunogenicity program**
 - Includes a risk assessment:

The risk-based immunogenicity program

- Analysing risk factors
- Designing a program according to the factors in question

Conclusions on the risk(s) of immunogenicity:

- **Impact on the benefit/risk**
- Tools to manage the risk
- **Address how to link adverse events to immunogenicity post-marketing**



Summary of the immunogenicity program



Why??

- Difficult to find the relevant data in the dossier



Unnecessary questions by the assessors

Risk based approach to the chosen immunogenicity program

- Are we taking immunogenicity too seriously?
- More emphasis on the risks of immunogenicity?
- Always be studied?
- Is there a double standard?
- Difference between manufacturing changes and biosimilar development?
- Should neutralising ADAs always be measured?
- PK+ADA samples during phase III: analysed and reported routinely or just "in case"?
- Typing of ADAs and epitope mapping: a waste of time?



What is the basic immunogenicity package ?

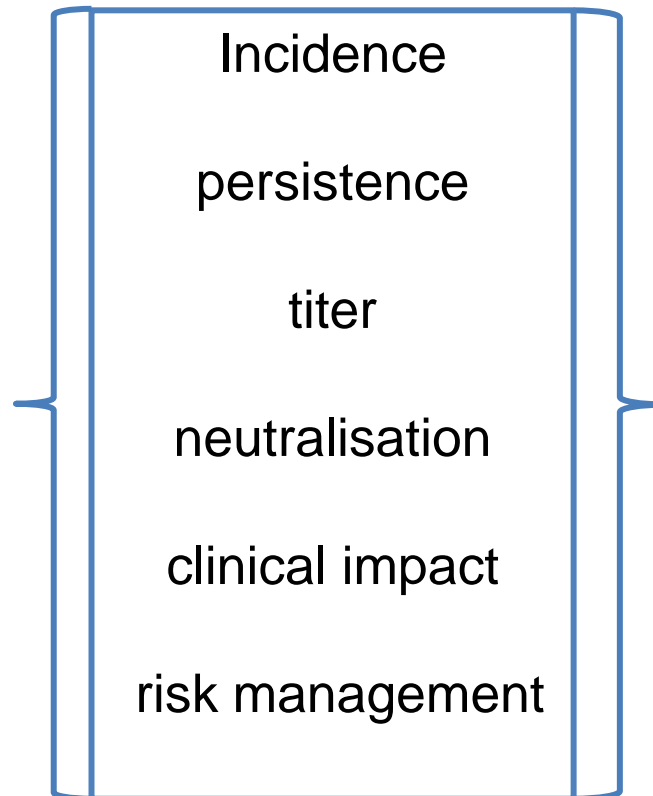
Low risk (e.g. etanercept)

Frequent sampling
only at the beginning

Analysis at the end
of a trial

Shorter follow up

Routine pharmaco-
vigilance (for immuno-
genicity)



High risk (e.g. epoetin)

More frequent sampling

Real time analysis

Longer follow up

Cell-based neutralisation
assay

Intensified clinical
monitoring

Post-marketing
immunogenicity study(ies)



Conclusions



- Planning and assessment of immunogenicity studies requires multidisciplinary team work
- It is impossible to study immunogenicity without valid assays for ADAs
- Immunogenicity assessment needs to be integrated into PK/PD, safety and efficacy
- An integrated summary of the immunogenicity program benefits applicants and assessors

Thank you for your attention!



Høgsfjord, Ryfylke, Norway, May 2016