European Guidance on Unwanted Immunogenicity of Biologicals

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Unwanted Immunogenicity

NIBSC
A centre of the Health Protection Agency

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Current Position

Testing for unwanted immunogenicity is integral to product development (clinical & post-marketing phase) for ensuring:

- **The clinical safety of a biotherapeutic**
- **Product Comparability**
- **When a Biosimilar product is developed.**

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

Guideline On Immunogenicity Assessment Of Biotechnology-Derived Therapeutic Proteins

NIBSC
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Health Protection Agency

- Executive Summary
- Introduction
- Scope
- Legal Basis
- Main Guideline Text
- Factors that may influence the development of an immune response against a therapeutic protein
  - Patient and disease related factors,
  - Product related risk factors of immunogenicity
- Non-clinical assessment of immunogenicity and its consequences
- Development of assays for detecting and measuring immune responses in humans.
  - Assay strategy
  - Antibody assays
  - Assay validation
  - Characterization of antibodies to a therapeutic protein
- Potential clinical consequences of immunogenicity
  - Consequences on Efficacy
  - Consequences on Safety
- Immunogenicity and Clinical Development
  - Rationale for sampling schedule and kinetics of the antibody response
  - Consequences on pharmacokinetics of the product
  - Methodology aspects to assess comparability of immunogenicity potential as part of a comparability exercise
  - Immunogenicity in paediatric indications
- Risk Management Plan
- References
- ANNEX 1 - Further details on methods for assessment and characterisation of immunogenicity
- ANNEX 2 - An example of a strategy for antibody detection and characterisation.

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’.
- **Concept paper agreed by BMWP Feb 2009.**
- **Sent for external consultation.**
- **Consultation completed/comments received June 2009.**
- **Drafting underway.**

Time line

- Drafting group was convened in October'09
- Comprises members from different member states
- Rapporteur – Robin Thorpe, NIBSC
- First draft prepared for :
  - Consideration at Biosimilar Medicines Working Party meeting in Feb 2010.
  - Draft finalised by end March.
  - Final draft considered by BMWP at end of June.
  - Sent for Internal Consultation in July.
  - Comment back in September.
  - External consultation- end 2010.

Concept Paper : Main Topics

- Points specifically relating to immunogenicity of mAbs which are not covered in the guideline on immunogenicity assessment
- Variability of immunogenicity of mAbs and its consequences.
- Particular problems experienced with screening and confirmatory assays used in assessing immunogenicity of mAbs.
- Appropriate strategies to be adopted for assessing the neutralizing capacity of antibodies induced against mAbs.
- Approaches which may be helpful in predicting unwanted immunogenicity of mAbs.
- Assessment of the clinical consequences of immunogenicity of mAbs, including a risk-based assessment of immunogenicity of mAbs and its problems. This could include also issues relating to immunogenicity of biosimilar mAbs.

mAb Immunogenicity Guideline:

- **Variability of immunogenicity of mAbs and its consequences.**
- **Approaches which may be helpful in predicting unwanted immunogenicity of mAbs.**
- **The clinical consequences of immunogenicity of mAbs.**
- **Problems experienced with screening and confirmatory assays used in assessing immunogenicity of mAbs.**
- **Assessing the neutralizing capacity of antibodies induced against mAbs.**
- **Risk-based Approach:**
  - -Risk of mounting an unwanted immune response
  - -The severity of clinical consequences of an immune response
  - -Consequences with regard to different risk classes

Unwanted Immunogenicity-EU Guidance

- **Other CHMP guidelines contain significant advice on unwanted immunogenicity.**
- **In particular the guidelines on Biosimilars address important immunogenicity issues-wider than just for biosimilars.**
- **These guidelines include the ‘overarching’ guideline, guidelines on preclinical/clinical and quality, and the product specific guidelines.**

Prediction of immunogenicity

- **Prediction of immunogenicity**
  - **In-silico and T cell methods are promising but information on the true clinical utility of these approaches in a prospective manner is lacking**
  - **While progress in this area is supported, it is premature to endorse the adoption of these approaches.**
  - **Approach advocated:**

    Human clinical data needed for all relevant indications of all mAb products – these data cannot be replaced by use of animal or in vitro or in-silico tools

Immunogenicity Testing

- So far, there is no perfect assay for determining the immunogenicity of therapeutics. Each assay has its own relative merits and weaknesses.
- May need to evaluate more than one assay platform, assay depends on therapeutic, assay conditions also vary.
- Select appropriate positive & negative antibody controls
- Assess sera – normal donors, patient sera
- Regulatory obligation to validate assays

Assays

- **Detailed testing strategy needed:**
  - **Assays are needed that are appropriate for detecting all of the specific human anti-mAb antibody responses. Issues relating to sensitivity, false-positive results are important.**
  - **The issue of drug interference and strategies for measuring abs in the presence of residual therapeutic e.g. acid treatment is very important.**
  - **Sampling strategies & Sample handling critical as is the distinction between transient vs persistent antibody responses.**
  - **Need for confirmatory assays.**

Neutralization assays

- **Detailed testing strategy:**
  - **Assessment of neutralizing activity crucial– Clarification of what is meant by 'neutralizing antibody' - abs directed against antigen binding site alone or also those interfering with immunobiological mode of action.**
  - **Requirement for Neutralization assays needs to be considered- Pros & Cons of Bioassays vs Competitive ligand binding (CLB) assays. In some cases CLB assays may be the method of choice.**
  - **Relevance of neutralizing antibody for safety and efficacy needs to be considered. Integration of ab data with PK/PD assessments required.**

Assay Validation

Assays need to be validated for their intended purpose.

Validation studies must be conducted to establish that the assays show appropriately linear responses to relevant analytes as well as appropriate accuracy, precision, sensitivity, specificity and robustness.

Problems encountered include matrix effects, selection of appropriate antibody controls and other reagents, residual product in samples, presence of pre-existing antibodies

Assays for assessing cell-mediated immune responses

The strategy for assessing cell-mediated immune responses induced by biologicals is generally less clear than for humoral responses.

Assays need to be developed or selected on a case-by-case basis if these are required.

In most cases, development of a mature IgG response implies underlying antigen specific helper T-cell involvement.

FDA & CHMP GUIDANCE

- Scope differs:
  - -FDA guidance is limited to assay development issues.
  - -CHMP guideline is more general & includes most topics important for immunogenicity assessment.

- But there is no major difference or conflict between the two guidances

FDA & CHMP GUIDANCE

- FDA guidance is more detailed. Includes more on assay validation.
- Includes some numerical guidance e.g. sensitivity for screening assay of 250-500 ng antibody/ml. This is not addressed in the CHMP guideline.
- Much in common with previous AAPS white papers.
- ‘Cut-points’ & related issues considered in some detail. This is not the case for the CHMP guideline.

‘Cut-point’ problems

- Can be problems if an inflexible approach is taken for ‘cut-point’ requirements.
- With a ‘good’ assay, there is a low matrix interference which results in a very low cut-point. This may cause problems i.e. a relatively high false positive rate.
- Also can be problems with acceptance criteria, due to the very low cut-point.
- For these reasons, the CHMP guideline does not make recommendations for cut points or detail other numerical requirements for assays.

Conclusions

Immunogenicity issues occur all along the life cycle of a product and particularly when :

- a new therapeutic protein is developed and used for various clinical indications
- a change is introduced e.g. process, formulation, storage conditions etc
- a biosimilar product is proposed

Assessment requires

- an optimal antibody testing strategy
- validated methodologies and reference standards

'Risk' assessment may be more problematical for mAb products than other products because of their complexity.

Risk may be variable, even for the same antibody used differently.

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