European Medicines Agency

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON IMMUNOGENICITY ASSESSMENT OF MONOCLONAL ANTIBODIES INTENDED FOR IN VIVO CLINICAL USE.

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1. INTRODUCTION

Unwanted immunogenicity is a significant problem with therapeutic biologicals. The clinical problems associated with unwanted immunogenicity vary in nature and incidence. The importance of the unwanted immunogenicity problem has led to the preparation and adoption of the 'Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins' by the CHMP (adopted April 2008).

Monoclonal Antibodies (mAbs) comprise a large important class of therapeutic biologicals. Different mAb products share some properties, but may differ in other aspects. Many mAb products are known to be associated with unwanted immunogenicity. Some issues pertaining to unwanted immunogenicity of mAbs differ in important aspects from those generally associated with therapeutic biologicals.

2. PROBLEM STATEMENT

The incidence of immunogenicity associated with mAbs differs greatly between products, patients and even in different studies with the same product and patient type. The complexity of structure of mAbs possibly explains at least some of this variation. In some cases, especially with humanised or human sequence mAbs the immune response is predominantly anti-idiotypic, which clearly can compromise clinical responses to the mAb. In some cases the induced antibodies reduce clinical responses to the mAb to such an extent that further therapy has to be terminated.

The very large number of mAbs in clinical development and undergoing regulatory scrutiny emphasises the critical need for provision of appropriate guidance on the unwanted immunogenicity of this large class of biologicals. Questions on immunogenicity are often asked during assessments of marketing authorizations for mAbs. The development of biosimilar mAbs is prevalent in various parts of the world, which again stresses the importance of having good guidance available, as unwanted immunogenicity is well known to also be a concern with biosimilars.

3. DISCUSSION

Several issues relating to unwanted immunogenicity of mAbs are covered in the Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins. However, this guideline is a general guidance and does not provide details on specific issues related to the immunogenicity of mAbs. MAbs are large complex biologicals and this complicates immunogenicity assessment. MAbs differ in many respects to smaller biologicals. The assays used to assess unwanted immunogenicity and its consequences are more problematic and difficult than those employed for small biologicals like GCSF, EPO and interferons (measuring antibodies against antibodies can be technically challenging). The nature of the clinical mode of action of mAbs implies that induced antibodies which block mAb binding to target are those which cause reduced clinical efficacy. Therefore, competitive ligand binding assays are often the neutralizing assays of choice for mAbs rather than classic bioassays. This distinguishes mAbs from other classes of biologicals.

Recently developed combinations of in-silico and T-cell based procedures are showing promise for predicting potential immunogenicity with some biologicals including mAbs. Identification of epitopes associated with induction or suppression of immune responses has been possible.

The great variability in the incidence and consequences of unwanted immunogenicity has led to proposals suggesting adoption of a risk-based approach for its assessment. Some products are considered to be low risk, whereas others may be associated with higher or very high risk. However, as mentioned previously, different mAb products differ greatly in their immunogenicity and its clinical consequences; therefore no single risk value can be applied to mAbs on a product-class basis. Risk, for mAbs needs to be considered on a case-by-case basis. This has been misunderstood by industry and others (mAbs have been considered as 'low-risk' as a class) and this requires re-appraisal and further guidance.

4. RECOMMENDATION

The Working Party on similar medicinal products (BMWP) recommends drafting a guideline on immunogenicity Assessment of monoclonal antibodies intended for in vivo clinical use**.**

The main topics to be addressed include:

- Points specifically relating to immunogenicity of mAbs which are not covered in the 'Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins'.
- 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.

5. PROPOSED TIMETABLE

Release for consultation in March 2009, deadline for comments 30 June 2009.

6. RESOURCE REQUIREMENTS FOR PREPARATION

An expert drafting group within BMWP in consultation with EWP, BWP, BPWP, SWP and PhVWP will develop this guideline. At least 2 formal meetings of the drafting group will be required in the margins of the working party meetings. A closed workshop may have to be convened prior to finalisation of the draft guideline.

7. IMPACT ASSESSMENT (ANTICIPATED)

Guidance on the investigation and assessment of immunogenicity of mAbs intended for in vivo clinical use will ensure a more rational and systematic approach to unwanted immunogenicity assessment, investigation and prediction for this large class of biologicals by industry, academia and regulators.

8. INTERESTED PARTIES

Competent authorities of the member states, and pharmaceutical industry.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

NA