European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON GUIDELINE ON IMMUNOGENICITY ASSESSMENT OF THERAPEUTIC PROTEINS

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END OF CONSULTATION (DEADLINE FOR COMMENTS)	1 June 2006

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1. INTRODUCTION

Treatment with therapeutic proteins may induce an immune reaction. Occasionally, this immune response is clinically significant.

Although it is required to study possible unwanted immune reaction to therapeutic proteins before licensing, problems are still encountered after licensing. Thus far, CHMP has not given general guidance for the investigation and assessment of immunogenicity of therapeutic proteins. Obviously, guidance on the investigation and assessment of immunogenicity may contribute to a more rational and systematic approach to the immunogenicity by the industry and the regulatory authorities.

This Guideline should be read in conjunction with the requirements laid down in the EU Pharmaceutical legislation and other relevant CHMP guidelines (see section 8).

2. PROBLEM STATEMENT

Patients treated with therapeutic proteins may develop an unwanted immune response to these products. The consequences of an immune reaction to a therapeutic protein range from transient appearance of antibodies without any clinical consequences to severe life threatening conditions.

The immune response against therapeutic proteins differs between products and patients since the immunogenic potential is influenced by many factors, such as the nature of the active substance, product- and process-related impurities, excipients and stability of the product, route of administration, dosing regimen, and target patient population. The patient-related factors may have a genetic basis, e.g. lack of tolerance to the normal endogenous protein, or acquired, such as immunosuppression due to the disease or its concomitant medication. There is considerable inter-individual variability in antibody response in terms of different antibody classes, affinities, and specificities.

Questions on immunogenicity are often raised during the assessment of the marketing authorisation applications for therapeutic proteins. In addition, significant immune-mediated adverse events have been reported post-licensing.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Detection and management of immunogenicity is an essential part of the development and post-marketing safety surveillance of biological medicinal products. Some guidance for the investigation of immunogenicity is available for certain product classes, such as coagulation factors and insulin as well as for biotechnology-derived similar biological medicinal products. The current guidance does not cover all aspects of the investigation of immunogenicity, such as risk assessment and development of assays, non-clinical and clinical studies, as well as post-marketing surveillance of immune-mediated adverse events. This multidisciplinary guideline would promote a systematic and integrated evaluation of immunogenicity.

4. RECOMMENDATION

The Working Party on similar biological medicinal products (BMWP) recommend drafting a guideline on immunogenicity assessment of therapeutic proteins.

The main topics addressed in this guideline are:

- Potential consequences of immunogenicity (efficacy and safety)
- Prediction of immunogenicity (product-, disease- and patient-related risk factors of immunogenicity)
- Development of assays (assay strategy, validation, standardisation, reference materials) for humoral and cellular immuneresponse

- Non-clinical aspects (potential use of in vitro and animal models)
- Characterisation of antibodies to a therapeutic protein (neutralising activities vs. binding, clinical relevant thresholds, antibody class, complement fixation)
- Pre-licensing signal detection (sampling schedule, kinetics of the antibody response, changes in clinical response, linking immunological findings to clinical events, laboratory parameters, impact on pharmacokinetics)
- Risk management / Pharmacovigilance (observational strategiesincluding monitoring of previously exposed patients)

5. PROPOSED TIMETABLE

Release for consultation on 23/02/06, deadline for comments 31/05/06, discussion in BMWP 06/06 to 07/06 discussion with BWP 07/06, proposed date for release of draft guideline 07/06, deadline for comments 10/06, re-discussion in BMWP 11/06 to 12/06, expected dated for adoption by Committee 01/07.

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 3 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 may contribute to a more rational and systematic approach to the immunogenicity by the industry and regulators.

8. INTERESTED PARTIES

Competent authorities of the member states, and pharmaceutical industry.

9. REFERENCES TO LITERATURE, GUIDELINES

- Directive 2001/83/EC, as amended.
- Part II of the Annex I of Directive 2001/83/EC, as amended.
- Guideline on similar biological medicinal products (CHMP/437/04/draft).
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CPMP/42832/05/draft).
- Note for guidance on repeated dose toxicity (CPMP/SWP/1042/99).
- Note for guidance on non-clinical local tolerance testing of medicinal products (CPMP/SWP/2145/00).
- Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus (CPMP/EWP/1080/02).
- Factor VIII / IX
- Pharmacokinetics
- Riskmanagement
- ICH S 6