EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 February 2014
EMA/275542/2013
Committee for Human Medicinal Products (CHMP)

Concept paper on the revision of the guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (CHMP/BMWP/42832/2005)

Draft

Agreed by Biosimilar Medicinal Products Working Party (BMWP)	January 2014
Adopted by CHMP for release for consultation	20 February 2014
Start of public consultation	25 March 2014
End of consultation (deadline for comments)	30 June 2014

The proposed guideline will replace 'Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins' (EMEA/CHMP/42832/2005)

Comments should be provided using this template. The completed comments form should be sent to BMWP.Secretariat@ema.europa.eu

Keywords	*Biological medicinal products, Biotechnology-derived therapeutic proteins, Immunogenicity, anti-drug-assays , risk factors, strategy for detecting immunogenicity*

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. Introduction

The Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins, CHMP/BMWP/42832/2005 laid down general recommendations for the performance of a systematic immunogenicity assessment from a marketing authorisation perspective. This guideline came into effect in June 2008. Since then CHMP has assessed a number of marketing authorisation applications (MAA) of biotechnology-derived therapeutic proteins. The Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use (EMA/CHMP/BMWP/86289/2010) came into force in December 2012.

2. Problem statement

Currently, hundreds of biological products, mainly biotechnology derived proteins are being developed for more than a hundred disorders.

At the same time, the knowledge on the assays, risk factors, and the potential consequences of unwanted immune responses, such as loss of efficacy, hypersensitivity, and cross-reactivity with endogenous protein, has accumulated. Considerable progress has been made in the development of better assays for antibodies against biologicals. During assessment of MAAs, CHMP has frequently raised questions related to the assays applied by the Applicants and the data on the clinical correlations of the induced antibodies. In addition, the section on non-clinical studies needs revision, taking account of the need to follow the 3 R principles (replacement, reduction and refinement). Since many risk factors of immunogenicity are known, it may be possible to estimate the risk level of a given product. Such analysis can be used to justify the selected immunogenicity strategy, i.e. the development of a suitable set of assays and the detection and clarification of the clinical significance of the observed anti-drug-antibodies both pre- and post-marketing. Large complex biotechnology-derived proteins and small proteins with a simple structure may require differential approaches to immunogenicity assessment. Comparisons of the immunogenicity of two versions of a product or two independent products (e.g. a biosimilar and its reference product) have certain specific aspects which need discussion. All these factors need to be considered when updating and revising the current guideline.

3. Discussion (on the problem statement)

The requirements of the immunogenicity assays may need to be defined more clearly since the CHMP has frequently had questions concerning the sensitivity of such assays and the use of ligand-binding and cell-based assays to demonstrate neutralizing antibodies. Most marketing authorisation applications lack a clear strategy to approach immunogenicity. Such a strategy should be based on a comprehensive analysis of all data that may be related to the immunogenicity.

The assessment of the immunogenicity risk level is a multifactorial and multidisciplinary exercise. Quality issues, such as impurities, aggregates, xenogeneic structures and leachables, need to be assessed. The dose, the frequency,,duration and route of administration, the underlying disease as well as the concomitant medication may modify the risk of immunogenicity.

The knowledge on the immunogenicity of the reference product may help to estimate the level of tolerance towards a particular protein. However, this needs care as the immunogenicity of the proposed biosimilar product may not be similar to the reference product. This has to be demonstrated

as part of the comparability assessment. The regulatory consequences of a different degree of immunogenicity, both increased and decreased, need to be considered.

Risk analysis might be used to estimate the extent of the immunogenicity studies as well as the length of the follow up pre- and post-licensing. Comparative immunogenicity studies may require more guidance on the assays and on the criteria for possible immune-related adverse effect.

4. Recommendation

The BMWP recommends revising and updating the Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins, CHMP/BMWP/42832/2005. The following topics should be addressed:

- More specific guidance for the presentation of immunogenicity data
- Requirements of data on antibody assays
- Role of *in vitro* and *in vivo* non-clinical studies
- Risk-based approach to immunogenicity
- Clinical data to study the correlations of the induced antibodies to allergic and anaphylactic/anaphylactoid reactions, delayed immunological reactions, pharmacokinetics, lack of efficacy
- Comparative immunogenicity studies
- Post-licensing immunological studies

5. Proposed timetable

Release for external consultation: 15 March 2014

Deadline for external comments: 30 June 2014

It is anticipated that the draft revised guideline will be released for consultation in 2014Q4.

6. Resource requirements for preparation

The BMWP experts will develop the revision of the guideline. At least one formal meeting of the drafting group will be required in the margins of the working party meetings.

7. Impact assessment (anticipated)

Anticipated benefit for industry (potentially reduced and/or specified requirements) and assessors of biological products. The revision is not aimed to increase the number of studies on immunogenicity. Instead, the aim is to increase the quality of studies and their clarity to the assessors.

8. Interested parties

Immunology/clinical immunology experts of the pharmaceutical industry and academia as well as CHMP and its working parties, especially SAWP and RIWP

9. References to literature, guidelines, etc.

The Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010)

Guideline on similar biological medicinal products (CHMP/437/04 Rev. 1)

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – quality issues (EMEA/CHMP/BWP/49348/2005)

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005)

ICH topic S6 – Note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95)

Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins

(CHMP/EWP/89249/2004)

ICH E10 Choice of control group in clinical trials (CPMP/ICH/364/96) Guideline on the choice of non-inferiority margin (CPMP/EWP/2158/99)