



European Medicines Agency
Evaluation of Medicines for Human Use

London, 20 July 2005
Doc. Ref.: CHMP/BWP/229472/2005

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**CONCEPT PAPER ON THE REVISION OF THE NOTE FOR
GUIDANCE ON ALLERGEN PRODUCTS (CPMP/BWP/243/96):
PRODUCTION AND QUALITY ISSUES**

AGREED BY BIOLOGICS WORKING PARTY	20 July 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	12 September 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 December 2005

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1. INTRODUCTION

Recent developments require the revision of the existing CHMP/BWP Guideline on Allergen Products¹: Since the approval and publication of this guideline in 1996, the scientific knowledge on structures, cross-reactivity, and stability of allergens has increased drastically, and many allergens have been produced as recombinant proteins. This scientific progress has several implications for regulation and standardisation of allergen products. Special emphasis has to be granted to recombinant allergen products. Therefore, the revised guideline should re-define the statements on batch-to-batch consistency, characterisation and use of in house reference preparations (IHR), control test as well as on safety and efficacy testing. Moreover it should be aimed at covering aspects specific for recombinant allergens that are not covered or specifically addressed by other guidelines on biotechnology-derived proteins²⁻⁵.

2. PROBLEM STATEMENT AND DISCUSSION

The Note for Guidance on Allergen Products¹ as well as the Monograph on Allergen Products⁶ contain regulations on the technical quality of allergen products that are based on natural allergen extracts. It is recommended to express the potency in units of biological activity, despite the fact that a wide range of different unit systems is currently used on the market. As a result, the strength of allergen products from different manufacturers cannot be compared directly. Recently, a research project funded by the EU was carried out to evaluate whether purified allergen molecules could serve as biological reference materials for improved standardisation of allergen products.⁷ The project was conducted as a feasibility study and included the ground work for developing candidate reference materials and validation of assays for major allergen quantification. The results indicated that it may be possible in the future to standardise allergen products in a uniform way, i.e. on the basis of mass units of major allergens. Existing regulations need to be revised to consider this possibility. Furthermore, the Note for Guidance on Allergen Products¹ accepts that data obtained in clinical trials with one member of a taxonomical family are extrapolated to other families, without providing further details of this concept. A detailed re-evaluation and elaboration of this concept is required.

Recombinant allergens and hypoallergenic derivatives thereof have been investigated as research tools for more than 15 years. So far, the only curative treatment of type I allergies is specific immunotherapy (SIT) with allergen extracts. An attractive hypothesis suggests that SIT with defined amounts of pure allergenic proteins may lead to increased clinical efficacy and safety. This effect may even be enhanced by using genetically engineered or chemically modified allergen variants with reduced IgE antibody binding capacity, but maintained T cell reactivity. Phase II and III clinical trials with recombinant grass pollen and birch pollen allergens, respectively, have been completed, with partially promising results. The first clinical trials with biotechnology derived mite allergens are in progress. Four companies are currently active in this field. Available data suggest that neither correct folding or preserved biological function of allergenic proteins, nor IgE binding capacity are required for the therapeutic effect, and results of recent studies provided evidence that an excellent therapeutic effect can be obtained with allergens that lack almost any IgE reactivity. Among the European regulatory framework for biotechnological products, Q6B² covers many aspects of recombinant allergens, but several specific issues such as potency testing, extent of structural characterisation, or factors related to expression systems need to be addressed for allergens.

3. RECOMMENDATION¹

The scope of the revised guideline will encompass: Production and quality issues concerning natural and biotechnology derived allergen products including derivatives with reduced IgE binding capacity

and / or enhanced immunogenicity as well as fusion constructs containing polypeptides derived from allergens as well as non allergenic functional polypeptides.

The following main topics were identified:

- Elaborate on requirements in allergen standardisation to change from potency units of allergen extracts to mass units of individual allergens.
- Re-define and elaborate in detail the concept of taxonomical allergen families. Define in detail phylogenetical relationships that are accepted for extrapolation of clinical data. Consider applying the principle of “allergen families”⁵ to biotechnology derived allergens.
- Define acceptance criteria for allergen mixtures from a single allergenic source and from different sources, respectively.
- Guidance is required on production related issues and expression systems for biotechnology derived allergens. Depending on the expression system used, the relevance of folding and posttranslational modification needs to be elaborated in keeping with the fact that the drug substance is intended for application in subjects susceptible to developing hypersensitivity reactions.
- Guidance is required on appropriate potency assays for batch release of natural and recombinant allergen products with reduced IgE binding capacity. So far, total allergenic activity is exclusively based on IgE binding measurements despite the fact that T cell stimulation capacity is considered to be of major importance for the therapeutic effect.
- Elaborate on the relevance of folding and posttranslational modification of allergens in regard to the establishment of batch control procedures.
- Formulation issues.
- Elaborate on stability testing of intermediate products (IMP) and end products.

4. TIMETABLE

It is anticipated that the draft revision of the guideline will be released for consultation by second quarter of 2006.

5. RESOURCE REQUIREMENTS FOR PREPARATION

The amended guideline will be developed by the CHMP Biologics Working Party. As the amendment might impact on other guidelines^{3,4,8} and also relevant clinical guidelines consultation with the relevant working parties concerned will be needed.

6. IMPACT ASSESSMENT

The guideline should provide improved guidance to Industry on the development of allergen products including products containing biotechnology derived proteins. It will result in a more consistent assessment of products by Regulators. This will contribute to improved standardisation of existing allergen products and to the availability of novel allergen products with enhanced clinical efficacy and safety to the market and thereby benefit public health.

7. REFERENCES

- 1 Note for Guidance on Allergen Products (CPMP/BWP/243/96).
- 2 Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Q6B; CPMP/ICH/365/96).
- 3 Note for Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (Q5C; CPMP/ICH/138/95).

- 4 Note for Guidance on Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines Used for Production of r-DNA Derived Protein Products (Q5B, CPMP/ICH/139/95).
- 5 Note for Guidance on Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (Q5D, CPMP/ICH/294/95).
- 6 European Pharmacopoeia Monograph on Allergen Products (1997:1063).
- 7 van Ree R. The CREATE Project: A new beginning of allergen standardisation based on mass units of major allergens. *Arb Paul-Ehrlich-Inst* 2003, 94, 70-74.
- 8 Note for Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (S6, CPMP/ICH/302/95).