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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 COMPARABILITY OF BIOTECHNOLOGY-DERIVED MEDICINAL PRODUCTS AFTER A CHANGE IN THE MANUFACTURING PROCESS

NON-CLINICAL AND CLINICAL ISSUES

AGREED BY BMWP	January 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	22 February 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	1 June 2006

The proposed guideline will replace guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance (CPMP/3097/02)

Comments should be provided to denisa.dechiara@emea.eu.int
Fax: +44 20 7418 8613

KEYWORDS	manufacturing process, change, comparability, non-clinical studies pharmacodynamic, efficacy, surrogate marker, safety

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.eu.int http://www.emea.eu.int

1. INTRODUCTION

The existing guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance (CPMP/3097/02) addresses two situations:

- When a change is introduced in the manufacturing process of a given product (either before the granting of a marketing authorisation or after the granting of a marketing authorisation [variation procedure]).
- When a product is claimed to be similar to another one already authorised in the EU after the expiry of the data protection period.

The second part of the guideline relating to "similar" products is now redundant since the issue is addressed in the new guideline on similar biological medicinal (biosimilar) products containing biotechnology-derived proteins as active substance – (non) clinical issues (EMEA/CHMP/42932/2005). Thus, the old guideline CPMP/3097/02 will be withdrawn and the requirements for a comparability exercise supporting changes in the manufacturing process will be addressed in a new guideline.

2. PROBLEM STATEMENT

Marketing authorisation holders frequently introduce changes in the manufacturing process of a given product (both before and after the granting of a marketing authorisation). The marketing authorisation holder will have to demonstrate or justify that both versions of the product have comparable quality, safety and efficacy. It is assumed that the product's physico-chemical properties and *in vitro*/*in vivo* biological activity are well characterised according to state of the art methods, but that these data are insufficient to exclude relevant changes in clinical efficacy and safety

3. DISCUSSION

For most changes to the manufacturing process, physico-chemical and *in vitro* biological testing can demonstrate that there is no adverse impact on the quality, safety and efficacy of a product. However, sometimes an effect on efficacy and/or safety can be expected or cannot be ruled out in spite of a state of the art physico-chemical and biological tests. In such cases, additional non-clinical and clinical studies will be necessary. The type and extent of such studies are variable and will dependent on numerous factors related to the drug substance and the drug product, to findings in the comparability exercise as well as to its clinical use. Thus, the required studies may include new tests in animal models or human pharmacokinetic or pharmacodynamic studies or clinical efficacy and/or safety studies.

This is a sequential process, beginning with quality studies (limited or comprehensive) and supported, as necessary, by non-clinical and/or clinical bridging studies.

This guideline will address the requirements for non-clinical and/or clinical bridging studies to demonstrate that the modification has no impact on safety and efficacy profile.

The main topics addressed in the guideline are the following:

Factors that trigger non-clinical and/or clinical testing

Non-clinical requirements

- Limitations of non-clinical tests in predicting human efficacy and safety
- Special features of non-clinical studies of comparability
- Types of pharmacological studies that may be used to demonstrate comparability
- Toxicological studies
- Value of new technology and animal models

Clinical requirements

Factors to be considered in designing a clinical comparability program

Role and special nature of pharmacokinetic studies

Pharmacodynamics

Design of pharmacodynamic studies and identification of relevant markers for primary and secondary pharmacodynamics, pharmacodynamic markers as surrogates for efficacy

Efficacy requirements

Design of efficacy study with both versions of the product, especially methodological considerations including:

- Selection of the most relevant patient population/therapeutic indication
- Selection of appropriate clinical endpoints / surrogate markers
- Study duration

Safety requirements

- Extent of the safety database
- Requirements for pre-approval safety evaluation
- Requirements for a pharmacovigilance risk management plan

4. RECOMMENDATION

The BMWP recommends drafting a guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process

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

The BMWP experts will develop the guideline. At least 3 formal meetings of the drafting group will be required in the margins of the working party meetings.

7. IMPACT ASSESSMENT (ANTICIPATED)

N/A

8. INTERESTED PARTIES

Competent authorities of the member states, and pharmaceutical industry.

CHMP and its working parties EWP, BWP, BPWP, SWP and PhVWP.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

- Topic Q5E, Step 4 Note for Guidance on Biotechnological/Biological Products Subject to changes in their Manufacturing Process (CPMP/ICH/5721/03 final approval by CHMP December 2004)
- Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance (CPMP/3097/02)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/42832/05)