The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

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CONCEPT PAPER ON THE DEVELOPMENT OF A COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP) GUIDELINE ON COMPARABILITY OF BIOTECHNOLOGY-DERIVED PRODUCTS

Background

In recent years, the CPMP and its BWP have been faced with a number of dossiers and situations where it was necessary to evaluate the comparability of biotechnology-derived products when changes are made in the production process either during the development or after the marketing authorisation has been granted. The same questions were also put by Company through the scientific advice procedure.

There are two possible situations both assessors and companies could be confronted with:

i) Comparability of a given product following changes made in its production process. The change can be proposed either during the development (process carried out during Research & Development) or after the grant of the Marketing Authorisation (currently approved production process).

1. Comparability of recombinant proteins, pertaining to the same molecular group, already produced by a manufacturer but newly developed by another manufacturer.

The issue of demonstration of comparability of Biotechnology-derived products in these situations, should be addressed in a specific guideline. To some extent, CPMP/BWP have already addressed the issue of comparability in the CPMP Note for Guidance on production and quality control of monoclonal antibodies.

Current status:

Currently ICH and CPMP guidelines provide guidance in terms of quality and specifications to set up for Biotechnological-Biological products (see list of documents below). In addition, Commission Regulations 541+542/95 dealing with variations lay down the approval process for granting variations and provide the requirements to be fulfilled for proposed changes for biological medicinal products. However, none of these guidelines, with the exception of the above-mentioned Note for Guidance on monoclonal antibodies, addresses the question of comparability in a comprehensive and specific manner.

On April 1996, the FDA released a "Guidance Concerning Demonstration of Comparability of Human Biological Products, including Therapeutic Biotechnology-Derived Products". However, the only aspect covered in the text deals with changes introduced in a given production process for a given product from a well identified manufacturer. The more general question on how to compare two biopharmaceuticals from different manufacturers was not covered.

Points to consider in the guideline:

It is proposed to develop a guideline to address the issue of demonstration of comparability for Biotechnology-derived products. The scope of the guideline should be, as a first intention, restricted to biotechnology-derived products (i.e. recombinant proteins), representing a somewhat homogeneous class of products, particularly in terms of production/purification processes.

Various points should be discussed in the guideline:

i) Physico-chemical and biological tests required to demonstrate structural equivalence of the two products.

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ii) Identification and assessment of the potential impact of changes made in the production process on the quality of the product, with special attention to:

- Pilot production vs. Full scale production
- Implementation of a new production site
- Change in the production process ; and particularly change in cell substrate or culture media
- Change in the purification scheme
- Change in the equipment and facilities

iii) To what extent "quality" tests, i.e. pertaining to part II of the dossier and including characterisation, physico-chemical tests, biological assays, are sufficient to demonstrate the comparability of two recombinant proteins and therefore limited clinical and/or toxicological studies are necessary.

- Preclinical and toxicological data, in particular in relation to changes in quality profile, addressing also the impurity profile;
- Clinical and tolerance data, in particular in relation to the neo-antigenicity of the new product.

iv) Where possible, decision tree(s) could be set up or proposed so as to guide the producer in proper analytical, preclinical and clinical development.

Action proposed:

Further to the CPMP agreement for the development of such a guideline, a drafting group should be appointed amongst the BWP members. A first draft will have to be prepared by the drafting group for finalisation by the BWP before release for consultation by the CPMP. Release for consultation could be envisaged in December 1998.

Contribution from the SWP and EWP is deemed necessary in the development of this guideline. Indeed, preclinical and/or clinical experiences gained with the reference product should also be considered in a way to anticipate any possible efficacy and/or tolerance problem with the new product.

References:

1. Biotech. Heading for Notice to Applicants
2. CPMP Guideline on Production and Quality control of medicinal products derived by recombinant DNA technology
3. CPMP Guideline on Production and Quality Control of Cytokine products derived by biotechnological process (Guide, addendum
4. CPMP/ICH Guideline Q5C on Stability testing of biotechnological-biological products.
5. CPMP/ICH Guideline Q6B on Specifications, tests and procedures for Biotechnological/Biological products.
6. FDA Guidance concerning demonstration of comparability of human biological products, including therapeutic Biotechnology-derived products (April 1996).
7. FDA interim definition of Well Characterised Therapeutic r-DNA derived products (Dec.1995).
8. CPMP Guideline on Production and Quality Control of monoclonal antibodies
9. Criteria for investigation of the product equivalence of monoclonal antibodies for therapeutic in-vivo diagnostic use in case of introduction of changes in the manufacturing process. G. Schäffner, M. Haase and S. Giess. Biologicals (1995) 23, 253-259.
10. Commission Regulations 541+542/95 dealing with variations (March 1995).
11. Guideline on dossier requirements for Type I variations