European Medicines Agency
Evaluation of Medicines for Human Use

London, 21 October 2004
CHMP/BWP/64/04

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER

ON THE NEED TO REVISE THE GUIDELINE ON PRODUCTION AND QUALITY CONTROL OF MONOCLONAL ANTIBODIES (3AB4A, *Revision December 1994*)

AGREED BY BIOTECHNOLOGY WORKING PARTY	SEPTEMBER 2004
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	OCTOBER 2004
START OF CONSULTATION	NOVEMBER 2004
END OF CONSULTATION	END OF JANUARY 2005

Public
7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 8447
E-mail: mail@emea.eu.int http://www.emea.eu.int

Concept Paper on the need to revise of the Guideline on Production and Quality Control of Monoclonal Antibodies (3AB4a, *Revision December 1994)*

1. Introduction and problem statement

Monoclonal antibodies (MAbs) are a class of highly innovative biotechnological products. They are characterised by:
-A specific structure, which is based on the immunoglobulin structure.
-A clearly defined functional activity, which is primarily based on a specific binding characteristic to a ligand (commonly known as the antigen).
In humans, antibodies appear as a polyclonal mixture of highly variable specificities and show a number of functions, among them the specific neutralisation of pathogens and the immunomodulation of cells of the immune system.
Production of hybridomas secreting MAbs was first described in 1975. The technology of creating MAbs (i.e. antibodies derived from one clone, directed against one specific antigen) was developed in the late 1970s and has opened up new possibilities for the treatment of diseases. The subsequent use of MAbs for scientific research and *in vitro* diagnosis is one of the successes of biomedical science.
The first MAb for pharmaceutical use was approved in 1986, but the developments in this field have been slow and difficult. However, in the last 2-3 years about 10 new products with a MAb as the active substance have successfully obtained a marketing authorisation. Moreover, a high percentage of proteins currently in phase II and III clinical studies are MAbs. It is clear that the field has now matured.

The maturation is due to the fact that a number of totally new and innovative techniques and procedures have evolved. A number of examples and their consequences are:
- New molecular biologic techniques for the humanisation of MAbs, or for the creating of human MAbs without the use of hybridoma technology.
- New analytical techniques allowing for detailed molecular characterisation of the MAb molecule, showing heterogeneity of these products.
-New manufacturing technologies and procedures, such as frequent use of contract manufacturers and development of generalised manufacturing procedures used for more than one product, including the use of generalised virus validation studies.
- Development of highly-adapted molecules such as fusion proteins, single-chain MAbs and bispecific or trifunctional MAbs.

However, regulatory work has not kept apace with the new and innovative developments in the field. Guidance on the subject of MAbs for pharmaceutical use dates back to 1994 (document III/5271/94, in volume 3A of The Rules Governing Medicinal products in the European Union).
It is expected that a significant number of new MAb-containing pharmaceuticals will be submitted to the EMEA for approval and scientific advice. The assessment of recently submitted MAbs has made clear that the many innovative developments in the field of MAbs are not reflected in the existing Guideline and therefore a revision of the Guideline is necessary.
The need for revision is further exemplified by the fact that the European Pharmacopoeia has adopted a general monograph on MAbs for human use in June 2004, which will come into force in July 2005; and a significant number of scientific conferences in this field that are currently held.

2. Discussion and recommendation

A complete and general revision and update of the Guideline for monoclonal antibodies is necessary.
It is proposed that the scope of the guideline will be ‘production and quality control of monoclonal antibodies’. The scope should include MAbs used for therapeutic and *in vivo* diagnostic use, and also

molecules clearly related to MAbs, such as MAb fragments, single-chain MAbs and bispecific or trifunctional MAbs, fusion proteins, and conjugates.
Besides a general revision of the whole text, the discussion should focus among others on the following specific issues:
- Requirements and acceptability for hybridoma-derived MAbs.
- Requirements and acceptability for murine (i.e. non-humanised) MAbs.
- Requirements for human, humanised and chimeric MAbs.
- The consequences of developments in analytical technology for microheterogeneity/product-related substances, glycosylation, identity testing, potency testing, etc.
- The consequences of developments in manufacturing technology for consistency of production.
- The consequences of the development of almost identical manufacturing processes for different MAbs (generalised manufacturing, sometimes described as 'generic' manufacturing), including the consequences for virus validation.
- Formulation issues (it has been noted in the past that aggregates tend to be formed in several MAb-containing products).
- Comparability issues, especially for the 'given product' situation.

In addition, a separate chapter of the Guideline will address issues specific to MAbs that are used for purification of other pharmaceutical products.

It is proposed to focus only on quality aspects. Some specific pre-clinical issues are addressed in ICH S6 *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (CPMP/ICH/302/95), while clinical issues are mainly addressed in Guidelines given in relation to the (proposed) clinical indication of the MAb. It is noted that specific pre-clinical or clinical issues identified, especially in relation to comparability, will be brought to the attention of the Comparability Expert Group for further discussion.

3. Timetable and resource requirements for preparation

A drafting group has been formed, which can meet on the margins of the BWP. It is aimed that a guideline for consultation can be adopted in the first half of 2005 by BWP/CHMP, followed by a 6-month consultation period.

4. Impact Assessment

The revision of the Guideline is part of the ongoing general development of suitable quality standards. It will result in a more consistent assessment of products by regulators, set clear standards and expectations for industry, and therefore be helpful in a harmonised regulatory policy.
The relatively small resource implications for preparation of a Guideline are fully justified and are compensated by the fact that application of a Guideline will make assessment easier and will result in less resources being needed during assessment.