Monoclonal Antibodies-CHMP Guidelines

Robin Thorpe PhD.,FRCPath
Head, Biotherapeutics Group, NIBSC

e-mail: Robin.Thorpe@nibsc.hpa.org.uk
COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE  
(CHMP)

GUIDELINE ON DEVELOPMENT, PRODUCTION, CHARACTERISATION AND  
SPECIFICATIONS FOR MONOCLONAL ANTIBODIES AND RELATED PRODUCTS

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRAFT AGREED BY BIOLOGICS WORKING PARTY</td>
<td>18 April 2007</td>
</tr>
<tr>
<td>ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION</td>
<td>24 May 2007</td>
</tr>
<tr>
<td>END OF CONSULTATION (DEADLINE FOR COMMENTS)</td>
<td>30 November 2007</td>
</tr>
<tr>
<td>AGREED BY BIOLOGICS WORKING PARTY</td>
<td>12 November 2008</td>
</tr>
<tr>
<td>ADOPTION BY CHMP</td>
<td>18 December 2008</td>
</tr>
<tr>
<td>DATE FOR COMING INTO EFFECT</td>
<td>1 July 2009</td>
</tr>
</tbody>
</table>

This guideline replaces the guideline on “Production and quality control of monoclonal antibodies”  
(JA4A)

This guideline replaces the quality requirements for monoclonal antibodies set forth in the guideline  
on “Radiotherapeutics based on monoclonal antibodies” (JAQ21A)

**KEYWORDS**

- Monoclonal antibody
- Recombinant protein
- Quality
- Characterisation
- Specification
- Hybridoma
**PRODUCTION AND QUALITY CONTROL OF MONOCLONAL ANTIBODIES**

<table>
<thead>
<tr>
<th>Guideline Title</th>
<th>Production And Quality Control Of Monoclonal Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legislative basis</td>
<td>Directive 75/318/EEC as amended</td>
</tr>
<tr>
<td>Date of first adoption</td>
<td>See previous titles/other references</td>
</tr>
<tr>
<td>Date of entry into force</td>
<td>This version adopted December 1994</td>
</tr>
<tr>
<td>Date of entry into force</td>
<td>July 1995</td>
</tr>
<tr>
<td>Status</td>
<td>Last revised December 1994</td>
</tr>
<tr>
<td>Previous titles/other references</td>
<td>Originally published as two guidelines: <em>Production and Quality Control of Human Monoclonal Antibodies</em> (July 1990) and <em>Production and Quality Control of Monoclonal Antibodies of Murine Origin</em> (June 1987). The previous reference of the combined version was III/5271/94</td>
</tr>
<tr>
<td>Additional Notes</td>
<td>This guideline outlines the requirements for murine, human and engineered monoclonal antibodies for therapeutic (including ex vivo application) and in vivo diagnostic use in humans. It concerns the application of Part 2, sections A, B, C, D and E of the Annex to Directive 75/318/EEC as amended with a view to the granting of a marketing authorisation for a new medicinal product.</td>
</tr>
</tbody>
</table>
Monoclonal antibodies for human use

Anticorpora monoclonal ad usum humanum

DEFINITION
Monoclonal antibodies for human use are preparations of an immunoglobulin or a fragment of an immunoglobulin, for example, Fab',2, with defined specificity, produced by a single clone of cells. They may be conjugated to other substances, including for radioisotopic labelling.

They can be obtained from immortalised B lymphocytes that are cloned and maintained as continuous cell lines or from RNA-engineered cell lines.

Currently available RNA-engineered antibodies include the following antibodies.

Chimeric monoclonal antibodies: the variable heavy- and light-chain domains of a human antibody are replaced by those of a non-human species that possess the desired specificities.

Humanised monoclonal antibodies: the 3 hypervariable regions (complementarity-determining regions) of non-human species for each chain are engineered into the variable domain framework of a human antibody; other sequence changes may be made to improve antigen binding.

Recombinant human monoclonal antibodies: the variable heavy- and light-chain domains of a human antibody are combined with the constant region of a human antibody. Recombinant antibodies obtained from cell lines modified by recombinant DNA technology also comply with the requirements of the monograph "Products of recombinant DNA technology" (0784).

This monograph applies to monoclonal antibodies for therapeutic and prophylactic use and for use as in vitro diagnostics. It does not apply to monoclonal antibodies used as reagents in the manufacture of medicinal products. Nor does it apply to monoclonal antibodies produced in animals, for which requirements are defined by the competent authority.

PRODUCTION
GENERAL PROVISIONS
Production is based on a seed-leaf system using a master cell bank and, if applicable, a working cell bank derived from the cloned cells. The production method is validated during development studies in order to prevent transmission of infectious agents by the final product. All biological materials and cells used in the production are characterised and are in compliance with chapter 5.2.8. Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products. Where monoclonal antibodies for human use are manufactured using materials of human or animal origin, the requirements of chapter 5.7.7. Final safety also apply. Where an immunogen is used, it is characterised and the method of immunisation is documented.

Process validation. During development studies, the production method is validated for the following aspects:

- consistency of the production process including fermentation, purification and, where applicable, fragmentation method;
- removal or inactivation of infectious agents;
- adequate removal of product and process-related impurities (for example, host-cell protein and DNA, protein A, antibodies, cell culture components);
- specificity and specific activity of the monoclonal antibody;
- absence of non-endotoxin pyrogens;
- reactivity of purification components (for example, column material), limits or acceptance criteria being set as a function of the validation;
- methods used for conjugation, where applicable.

Product characterisation. The product is characterised to obtain adequate information including: structural integrity, isotype, amino-acid sequence, secondary structure, carbohydrate moieties, disulphide bridges, conformation, specificity, stability, specific biological activity and heterogeneity (characterisation of isoforms). A battery of suitable analytical techniques is used, including chemical, physical, immunochemical and biological tests (for
• CHMP guidance is a ‘guideline’.
   It gives advice, in some detail.
   It does not have legal ‘force’.

• EP monograph is very general.
   It has legal ‘force’ in Europe- products must comply, unless there is appropriate justification for non-compliance.
CHMP guidance for mAbs

There is considerable continuity between the new mAb guideline & previous guidelines for mAbs. It updates previous guidelines, and the emphasis has changed to reflect the current situation with mAbs intended for clinical use.
This guideline covers principles and general requirements for development, production, characterisation and specifications for monoclonal antibodies to be used as, or in the production of, human medicinal products.
This guideline addresses quality issues for the marketing authorisation of monoclonal antibodies derived from a monoclonal cell line, and intended for therapeutic and prophylactic use (including ex vivo application), and in vivo diagnostic use.
The structure of the monoclonal antibody should be justified with respect to its mechanism of action, biological activity and stability. This justification should at least include discussion on the suitability of the product’s immunochemical properties (e.g. affinity, cross-reactivity, isotype, allotype) and the importance and integrity of effector function.
Furthermore, the risk of inducing antibody responses in patients should be carefully considered, especially when the product does not have a high homology with human immunoglobulin, or when potentially immunogenic epitopes are identified in the structure, as it may result in clinical adverse reactions and/or modify the therapeutic potential.
• General considerations
• Platform manufacturing:
  ‘Some manufacturers have gained considerable experience in the production of monoclonal antibodies, and have developed a production strategy based on similar manufacturing processes (i.e. using a predefined host cell, cell culture and purification process). This approach is often referred to as “platform manufacturing”.'
CHMP guidance for mAbs - characterisation of monoclonal antibodies

- Physicochemical characterisation
- Immunological properties
- Biological activity
- Purity, impurity and contaminants
- Quantity

‘The monoclonal antibody should be characterised thoroughly.......in line with ICH Q6B guideline.’
‘Specifications are one part of a total control strategy designed to ensure product quality and consistency, and when tested, the product should be in compliance with its specification.’

Identity, Purity and impurities, Potency, Quantity & General tests.

‘Visible and sub-visible particulate matter in drug product should comply with the requirements set forth in the European Pharmacopoeia.’
In addition to intact, non-modified monoclonal antibodies, the scientific principles described in this document can be applied to other monoclonal antibody related products, such as antibody fragments (including single-chain variable fragment (scFv)), fusion proteins, conjugated monoclonal antibodies, bispecific antibodies and radiolabelled antibodies. However, their applicability will be determined on a case-by-case basis, based on the specific properties of the product.
Members of the CHMP mAb drafting group.
Members of the EP mAb working party.
Colleagues from industry, academia, regulatory agencies.