European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE NEED TO REVISE THE GUIDELINE ON THE USE OF TRANSGENIC ANIMALS IN THE MANUFACTURE OF BIOLOGICAL MEDICINAL PRODUCTS FOR HUMAN USE (3AB7A OF JULY 1995)

AGREED BY BIOTECHNOLOGY WORKING PARTY	May 2009
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	25 June 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 September 2009

The proposed guideline will replace guideline 3AB7A.

Comments should be provided using this template to alexis.nolte@emea.europa.eu

KEYWORDS	*Transgenic animals*

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. INTRODUCTION

Recombinant proteins for medicinal use are routinely produced in bacterial or mammalian cell lines. The regulatory requirements to make and test the production lines and cell banks, and the subsequent manufacture and testing of the medicinal product are well established. Many relevant Guidelines are available for production in cell lines.

An alternative production platform for recombinant proteins is transgenic animals, where a foreign gene, which codes for a therapeutically useful protein, is inserted into the genome of the chosen species and is expressed under the close control of a promoter. The recombinant protein is generally expressed in some easily harvested body component such as milk or eggs and does not harm the animal.

Several advantages are associated with the use of this production platform, including potentially very high expression levels of the recombinant protein, easy scale up of production by breeding a larger number of animals, and relatively low production costs when compared to conventional methods since no up-stream fermentation equipment is required. Additionally, post translational modifications may result in product which closely resembles the natural protein since they are produced in whole mammals instead of isolated cell cultures.

2. PROBLEM STATEMENT

A guideline was prepared by CPMP and entered into force in July 1995 (3AB7A). Although it contains advice which was useful for a technology platform which was in its infancy, since it came into force, this production method has progressed significantly and the guidance has not been revised to take account of these advances.

The current guideline was prepared at a time when the scientific possibilities for transgenic animals were being investigated and no product had been generated for commercial or clinical trial purposes. In addition, many relevant guidelines, such as the ICH Q5 series had not been prepared.

Since the publication of the guideline, many therapeutic transgenic proteins (such as C1 Inhibitor, monoclonal antibodies, TPO and fibrinogen) have been produced in a number of different species (such as mice, goats, sheep, rabbits and cows) and using varying genetic elements. The material has been tested pre-clinically and clinically, and two products have been evaluated by CHMP through their Marketing Authorisation Applications, with one (to date) gaining approval.

The production of medicinal proteins in transgenic animals raises its own set of regulatory and scientific issues, such as the lack of a cloned cell bank, a level of variability in every production animal, a unique position regarding pathogen safety and a new spectrum of host related impurities.

With the experience gained in recent years in this field, especially through the assessment of applications for Marketing Approval, it is now possible to put the clinical relevance of many unique quality issues into perspective and to update the guideline to provide relevant and important guidance. The main aim of the revision is to adapt aspects of the quality guidance already in place for other production systems to the special case of transgenic animal systems.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

It is proposed that the scope of the guidance covers the quality issues regarding biological active substances produced by the expression of one or more transgenes stably located in the genome of animals. Production using cloned animals falls outside the scope.

The following improvements to the published guideline have been identified.

- The current document contains too many references to the benefits of transgenic technology but is not sufficiently detailed technically. A complete re-write to bring the structure of the document in line with the current format of CHMP guidance documents is needed.

- The lay-out of the document is not logical or easy to follow. It is not broken down into logical sections which follow CTD headings and concepts.

- There is no specific section on pathogen safety.

- There is no discussion of specific Quality systems, particularly for generation of transgenic lines, breeding and maintenance of production animals.

- A discussion on product characterisation is omitted.

- Breeding strategy is not mentioned, nor the concept of master and working cell/transgenic banks.

- Control of active substance or raw material is not adequately covered.

- Advice on residual Host Cell Proteins and DNA is incomplete.

- Since products from transgenic animals are (to date) the product of sexual reproduction, and not of cloned animals, the potential inherent variability of transgenic proteins needs to be explicitly discussed and the regulatory requirements to map this variability should be updated.

- Advice on the information which is required regarding development genetics is confusing and should be clarified.

- Advice is given that material from different genetic lines should not be mixed when producing product for a single license. This advice needs to be reviewed in light of more recent regulatory considerations.

4. RECOMMENDATION

The Biologics Working Party recommends developing a guideline on the use of transgenic animals in the manufacture of biological medicinal products for human use to replace the existing guideline.

5. PROPOSED TIMETABLE/RESOURCE REQUIREMENTS FOR PREPARATION

A drafting group should be formed, which will meet at dedicated drafting group meetings and also in the margins of BWP meetings and via remote conferencing. It is aimed that a guideline for consultation can be adopted in the first half of 2010 by the BWP/CHMP.

6. IMPACT ASSESSMENT (ANTICIPATED)

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.

7. INTERESTED PARTIES

The Inspectors Working Party will be consulted during preparation of this guideline and a draft guideline will be released for public consultation of interested parties.

8. REFERENCES TO LITERATURE, GUIDELINES ETC

Guideline on the ‘Use of Transgenic Animals in the Manufacture of Biological Medicinal Products for Human use’ 3AB7A (http://www.emea.europa.eu/pdfs/human/bwp/3ab7aen.pdf).