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

London, 6 December 2006

Doc. Ref. EMEA/CHMP/BWP/495530/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE REVISION OF THE NOTE FOR GUIDANCE ON PLASMA-DERIVED MEDICINAL PRODUCTS

AGREED BY BIOLOGICS WORKING PARTY (BWP)	December 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	14 December 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 March 2007

The proposed guideline will replace NfG on plasma-derived medicinal products (CPMP/BWP/269/95 rev. 3)

Comments should be provided to Olga.McIntosh@emea.europa.eu / Fax +44 20 7418 85 45

KEYWORDS	*Plasma-derived medicinal products, source material, plasma master file, manufacture, quality control, validation studies*

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

Two major issues necessitate the revision of the Note for Guidance (NfG): the knowledge on the viral safety issues of plasma-derived medicinal products is still in evolution and the legislative situation has changed significantly during the last few years.

During these past years, the knowledge on viral safety issues increased as more experience was gained in relation to virus removal/inactivation. Discrepant assessments of the virus validation part of Marketing Authorisation Applications became evident between member states in the Mutual Recognition Procedure, highlighting the need of the review of the NfG.

The principle of a plasma master file was introduced in Part III of Directive 2003/63/EC, amending Directive 2001/83/EC relating to medicinal products for human use.

Collection and testing of human blood and blood components have to comply with the 'Blood Directive' 2002/98/EC and the related Commission Directives 2004/33/EC, 2005/61/EC and 2005/62/EC

There are still many uncertainties in relation to the risk of Creutzfeldt-Jakob disease (CJD) transmission via blood and blood components. The most recent knowledge should be taken into account when revising the document.

2. PROBLEM STATEMENT

The revised version of the note for guidance was adopted by CPMP in January 2001. Since then several EU directives were adopted in relation to medicinal products and more specifically on blood/plasma and on the use of plasma as starting material for the production of medicinal products. The NfG needs to be adapted to the new legislative situation, the new CHMP guidelines, and the scientific knowledge in relation to viral safety and human TSEs.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

The NfG covers plasma-derived medicinal products and more specifically the source material (plasma master file), the manufacture, the quality control and the validation studies, with special attention to viral inactivation/removal.

Some issues in the field of plasma-derived medicinal products are continuously changing as more insight has been gained on the techniques, e.g. virus removal or inactivation. New emerging transmissible diseases can make additional safety measures necessary. Furthermore, there was an update on the legislation of medicinal products and more specifically on plasma-derived medicinal products.

In general, the requirements for quality set out by this Note for Guidance are still valid, but would benefit from revision to

- Update the references to European legislation on medicinal products in general and on plasma master file in particular. Compliance with the blood directives should be assured.
- Update in relation to the new EMEA/CHMP guidelines on plasma master file, virus validation, Creutzfeldt-Jakob Disease etc.
- Update of chapter concerning viral validation, to facilitate common assessment of MAA of plasma-derived medicinal products.
- Update of information on the test methods and their validation.
- Update on NAT testing.

4. RECOMMENDATION

The BWP recommends revision of the Note for Guidance on plasma-derived medicinal products, in view of new legislation and new insights in viral safety. Also the knowledge concerning Creutzfeldt-Jakob disease has to be taken into account when reviewing the document.

1. **Introduction**: the reference to the directives should be updated and reference to the blood directive should be introduced. Reference to (v)CJD and infectivity in blood should be included.

2.3. **Collection and control of source materials**: possibility to describe the starting material (Human plasma) in a plasma master file (PMF) was introduced by Directive 2003/63/EC, amending Directive 2001/83/EC.

2.3.4. Suitability of donors and screening of donations: reference to the Directives 2002/98/EC and 2004/33/EC. Reference to the increasing use of NAT testing on minipools as part of donation screening.

2.3.5. Data on epidemiology of infections transmitted by blood: reference to Guideline on Epidemiological Data on Blood Transmissible Infections.

2.3.6. Post-collection information system: reference to Guideline on the Scientific Data Requirements for Plasma Master File (PMF) and to CHMP Position Statement on Creutzfeldt-Jakob Disease and Plasma-Derived and Urine-Derived Medicinal Products

2.3.7. Bags for collection and storage of blood and plasma: change to be in agreement with Guideline on the Scientific Data Requirements for Plasma Master File (PMF).

3. **Manufacture**: adaptation of reference to directives.

3.2.2. Virological tests: deletion of plasma pool testing for anti-HCV, introduction of reference to validation guidelines for viral markers.

3.2.3. Nucleic Acid Amplification Technology: Update on NAT testing for viral markers including reference to the requirement of NAT for B19 DNA for plasma pools used for the production of SD plasma and anti-D immunoglobulins. Consideration of extension of NAT for B19 DNA to all plasma pools.

3.2.4. Manufacture of intermediate plasma fractions: update the reference given for source material to Guideline on the Scientific Data Requirements for Plasma Master File (PMF).

3.2.5. Albumin and other plasma-derived products used in the manufacture and formulation of medicinal products: deletion of date of January 1999 concerning transitional period and update statement on albumin in line with the current CHMP Position Statement on Creutzfeldt-Jakob disease and Plasma-derived and Urine-derived Medicinal Products.

3.3.2. Viral inactivation/removal procedures: reference to Annex 14 to be checked if still applicable; need to change the text on solvent/detergent treatment; adapt text on virus removal by filtration.

4. **Quality Control**

4.2. Quality control of products: clarify text regarding European Pharmacopoeia.

5. **Validation studies**

5.2.1. Manufacturing process design: add information on viral safety evaluation in relation to the statement on viral safety in the SPC (Guideline on Assessing the Risk for Virus Transmission - New Chapter 6 of the NfG on Plasma-Derived Medicinal Products).

5.2.2. Choice of viruses for use in validation studies: update is needed based on acquired knowledge and new techniques.

5.2.3. Strategy for introduction of additional process steps for inactivation and removal of viruses: updating.

5.4. **new point**: investigation of the manufacturing process for plasma-derived medicinal products with regard to vCJD.

6. **Guideline on assessing the risk for virus transmission** (new chapter 6 of NfG)

5. PROPOSED TIMETABLE

It is anticipated that the revised draft guideline will be released for consultation in the first quarter of 2008.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The guideline will be revised by the BWP. A rapporteur and experts will be appointed to participate in the drafting group. It is anticipated that the revision will require at least three dedicated drafting group meetings. Additional break out sessions will be organised in the margin of the BWP plenary meetings if required.

7. 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 marketing authorisation applications by regulators, set clear standards and expectations for industry, and therefore be helpful in a harmonised regulatory policy.

The relatively small resource implications for revision of the guideline are fully justified and are compensated by the fact that the application of the guideline will harmonise the assessment.

8. INTERESTED PARTIES

The interested parties identified for this guideline are the competent authorities of the Member States and the pharmaceutical industry. Concerns of interested parties raised during a 6-month public consultation of the revised document will be considered before finalisation of the guideline.

The following concerned EMEA working parties will be consulted before release of the revised draft: Blood Products Working Party.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

Directive 2001/83/EC on the Community code relating to medicinal products for human use, as amended.

Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use.

Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC

Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components.

Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events.

Commission Directive 2005/62/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments.

EMEA/CHMP/BWP/298388/05 Guideline on Validation of Immunoassay for the detection of antibody to Human Immunodeficiency Virus (Anti-HIV) in Plasma Pools (CHMP adopted September 2006)

EMEA/CHMP/BWP/298390/05 Guideline on Validation of Immunoassay for the detection of Hepatitis B Virus Surface Antigen (HBSAG) in Plasma Pools (CHMP adopted September 2006)

EMEA/CPMP/BWP/125/04 Guideline on Epidemiological Data on Blood Transmissible Infections (CHMP adopted January 2005)

CPMP/BWP/5180/03 Guideline on Assessing the risk for Virus Transmission - New Chapter 6 of the NfG on Plasma-derived medicinal products (CHMP adopted October 2004)

EMEA/BWP/5136/03 Guideline on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with Regard to VCJD risk (CHMP adopted October 2004)

EMEA/CPMP/BWP/2879/02 *Revision 1* CHMP Position Statement on Creutzfeldt-Jakob disease and Plasma-derived and Urine-derived Medicinal Products

CPMP/BWP/3794/03 *Revision 1* Guideline on the Scientific Data Requirements for Plasma Master File (PMF) (CHMP Adopted November 2006)

CPMP/BWP/4663/03 Guideline on Requirements for Plasma Master File (PMF) Certification (CPMP adopted February 2004)

CPMP/BPWG/BWP/561/03 Note for Guidance on the Warning on Transmissible Agents in SPCs and Package Leaflets for Plasma-derived Medicinal Products (Adopted October 2003)