

## **PPTA Position Paper European Consultation on the Future of Pharmaceuticals for Human Use**

The Plasma Protein Therapeutics Association (PPTA) welcomes the initiative from the European Commission to consult stakeholders in the context of its consultation on the future of pharmaceuticals for human use dated 19 July 2007.

PPTA is the primary advocate for the world's leading producers of plasma-derived and recombinant analogue medicinal products. The medicines produced by PPTA members are used to treat patients suffering from rare life-threatening and/or life-impairing disorders and serious medical conditions including bleeding disorders (e.g. Haemophilia), immune system deficiencies (e.g. Primary Immunodeficiencies), auto-immune diseases, burns and shock.

PPTA is pleased to share its views on behalf of the plasma protein therapeutics industry regarding the following key questions outlined in the Commission's consultation paper:

### ***1. Do you agree with the analysis of the main challenges outlined above? Do you see other challenges?***

PPTA agrees with the Commission that regulatory harmonization is needed to allow proper implementation and interpretation of Community legislation by Member States in order to optimize the free movement of medicinal products.

This is of particular relevance for the plasma protein therapeutics industry where regulatory barriers are a recurring issue:

**Variations regulations:** PPTA has serious concerns about the impact of the "Commission Regulations (EC) No 1084/2003 and (EC) No 1085/2003" and the related "Guideline on dossier requirements for Type IA and Type IB notification (July 2003)" on the availability of life-saving biological therapies. We strongly object to the fact that the regulations and Guideline have become significantly more restrictive for biological medicinal products: according to the annex 1 of the new regulations the exceptions for biologicals have increased from 6 to 18. The consequences of these measures are that for biologicals, Type II variations are almost automatically required by the Member States and by EMEA. These stricter requirements can frequently not be justified, because of a lack of impact on the safety and efficacy of the final product. In addition, the associated fees put an unjustified financial burden on the manufacturers.

The situation is further exacerbated due to inconsistent implementation and interpretation by the different Member States. This has resulted in delays of up to one year. PPTA and other associations representing manufacturers of biological products

have alerted the Commission to this situation already in 2004 and 2005. We appreciate the fact that a revision of the two regulations has commenced in 2006 and we hope that the revision is performed as quickly as possible. This is of particular importance in view of the planned implementation of the concepts of ICH Q8, Q9, and Q10, which, in our view, is inefficient without the removal of the disincentives imposed on manufacturers of biological products by the variations regulations. PPTA member companies are happy to embrace the concepts stipulated in the ICH documents when the regulatory environment allows implementation without unnecessary hurdles and costs.

**National licenses:** PPTA would also like to draw the attention of the Commission to difficulties encountered with receiving a national license after completion of an MRP. The granting of national licenses following a successful closure of a mutual recognition procedure is suggested within a timeframe of 30 days per Notice to Applicants. However in practise in some Member States it takes about 3 years to get a national license. Mechanisms should be put in place to allow for an automatic grant of licenses after a defined period, eg. 3 months after closure of the MRP. This is important for the number of products that are not eligible for the decentralised or centralised procedure. The European Commission should follow-up with Member States after the timeframe of 30-days to review the status of the procedure and to ensure a speedy process of granting a national license.

A similar mechanism would also be advisable for the approval of variations through the MRP. In our experience MSs release national approvals at different times after the end of a procedure. Ideally it should be possible to implement the variation at the end of the procedure. National Authorities could continue issuing national approvals, if they choose to do so, but reporting the end-of-procedure date.

***2. Do you see other areas than those already targeted by the Commission where regulatory action should be taken?***

PPTA would like to bring to the attention of the Commission the following regulatory issues which remain areas of concern:

**2° step for EMEA certified PMFs:** PPTA would respectfully like to point out that the 2° step for EMEA certified PMFs is still an issue of greatest concern, because it is not working according to the intended spirit of facilitation of procedures. Most Member States have obviously not understood the concept and require a Variation Type II instead of a purely administrative procedure. Since such a variation has to be filed on annual basis, the imposed regulatory burden and associated costs are unacceptable for PPTA's member companies. We strongly recommend providing detailed and unambiguous instructions to the Member States.

**Active Substance Master File (ASMF) concept:** PPTA has concerns about the impact of the EMEA's position that the Active Substance Master File (ASMF) concept should not be applicable to biological active substances. This would force manufacturers of biological active substances to provide full details of all quality-related data to MA applicants who use these substances for the manufacture of their products.

[Ref. to CHMP Monthly Report of 29 October 2004 (EMEA/CHMP/119155/2004)] MAHs are advised that the concept of ASMFs, as laid down in Directive 2001/83/EC, cannot be applied in the context of biological medicinal products. The characterisation and determination of biological active substances' quality requires not only a combination of physico-chemical and biological testing, but also extensive knowledge of the production process and its control. The MAH/applicant for a biological medicinal product could therefore not comply with the requirement to "take responsibility for the medicinal product" without having full and transparent access to these quality-related data. The use of an ASMF would prevent such access, and should therefore not be allowed for biological active substances. In addition, active substances, which are present in certain medicinal products such as vaccines or cell-therapy medicinal products, do not fit with the concept of a "well-defined" active substance.]

The partition of the active substances documentation is a standardised and generally accepted modus operandi in order to allow pharmaceutical companies to trade with active substances among each other without forcing the manufacturer of the active substance to disclose confidential industrial intellectual property to (potential) competitors. Moreover, since active substances are often equivalent or similar to other medicinal products marketed by the manufacturer, disclosure of confidential know-how does not only concern the protected documentation for the active substances concerned but also confidential information of other licensed products from the manufacturer. Thus, the request to disclose full details of the quality part to applicants constitutes - at least indirectly - a governmental encroachment on manufacturers' fundamental property rights as recognised by the European Court of Justice. Such an encroachment is considered to be legally inadmissible unless specifically authorised by an applicable legal norm.

However, neither the quoted announcement of the CHMP (which merely describes the CHMP's current position) nor the quoted Directive 2001/83/EC provide a legal basis for this request. The Directive requires that "the manufacturer shall provide the applicant with all data, which may be necessary to take responsibility for the medicinal product". This is ensured on the basis of the ASMF concept by supplying the applicant with the applicant's part of the ASMF including the manufacturer's certificates of analysis, by appropriate change control procedures agreed between the parties, and through the continuous monitoring of the suitability of the active substance by the applicant's quality control department. Additionally, applicants may have insight into the manufacturer's documentation through respective audits at the manufacturer's facilities. Finally, all safety and quality relevant data are assessed by competent authorities during the licensing process. The disclosure of additional confidential information would not reduce the risk of patients treated with the medicinal product to suffer from an adverse event and thus would have no provable effect for enhancing public health.

The new position of the EMEA will prevent manufacturer of biological active substances in the future from selling their products to potential competitors and from entering collaboration projects, especially in the area of potential high tech products. Consequently, the EMEA's new approach risks to establish a new barrier to the free

movement of pharmaceutical goods within the Common Market and to prevent the European pharmaceutical industry from gaining a global leading role for the development and manufacturing of innovative pharmaceutical products. Therefore, our recommendation is to maintain the validity of the regulatory framework for ASMF also for biological products.

**Revision of Annex 19 to the GMP Guide:** During the last revision of the Annex 19 PPTA has already requested to remove the requirement for storage of retention samples to perform sterility and pyrogen tests, because repetition of the sterility test in reference samples is of limited value. Plasma protein therapies are manufactured from human plasma and are thus of limited availability. The amount of samples needed to fulfil this requirement is very high and the medicinal product is not available to patients in need of these often life-saving therapies. We believe that the decision to cancel the sterility test from the "retest program" should not be left to single competent authorities (in the form of an "exception") but should be made a general statement in the frame of this Annex 19.

**Patient consultation requirements:** The "Guidance concerning the patients' consultation requirements for the package leaflet (Article 59(3) and 61(1) of Directive 2001/83/EC as amended by Directive 2004/27/EC" does unfortunately not allow any exceptions for medicines which are administered only by health care professionals (e.g., intensive care medicines like Human Albumin solutions or thrombolytics). Furthermore, there are no exceptions for medicines for target patient groups that have regularly undergone special training before administering their special therapies. We therefore strongly recommend excluding from this Guidance/Guideline all hospital-only medicinal products / intensive care medicines (namely Human Albumin solutions and thrombolytics) as well as those patient groups, who have undergone a special training or education before taking a medicine in self administration, as outlined above.

***3. What would you suggest as concrete measures to ensure the safety of medicines supplied in the EU, addressing in particular counterfeit medicines and provision of high quality and affordable medicines also to third countries?***

Currently no harmonised identification or barcode system is available for pharmaceutical products in the EU. Each Member State has own systems of bar codes. There is an enormous potential for efficiency gains by harmonisation of these systems. This has also relevance to the product safety. Single Member States are planning to introduce national measures to prevent counterfeiting and allow for tracking products through the supply chain. However, no unique safety system for codification of the products exists throughout Europe. Different systems are under discussion and evaluation, e.g. the 2 dimensional bar code system and RFID. Taking the increasing counterfeit cases into account the pressure on pharmaceutical industry to implement safety systems is increasing while there is trend for disharmonisation driven by the Member States.

Under the current circumstances the following support is requested to improve and accelerate implementation of the safety systems:

- Guidance for a Pan-European unique and coherent product authentication and identification strategy/system;
- definition of a coding/serialization system to be used uniquely in all European countries covering the distribution chain from manufacturer to the customer define a regulatory framework/requirements for implementation of this system;
- the costs for implementation of the coding system should be kept at a minimum;
- Global harmonization of the systems as part of ICH and WHO initiative;

#### ***4. What can be done to improve Europe's international competitiveness?***

The proposed changes under items 1 to 3 will improve Europe's competitiveness through increased efficiency of regulatory processes.

#### ***5. What can be done to foster convergence and transparency as regards pricing and reimbursement in the EU?***

Reimbursement policies are a key issue facing the plasma protein therapeutics industry. Indeed it is important to understand that the production of plasma-derived medicinal therapies is a unique enterprise where several interdependent therapies are produced from a single starting material, human plasma, which is very different from the chemically based pharmaceutical industry. The biological nature and the scarcity of human plasma as raw material provide particular challenges to the plasma protein therapeutics industry which need to be taken into account into EU national reimbursement policies. Direct manufacturing costs including those of the raw material (human plasma) account typically for up to 70% of the purchase price compared to less than 20% for chemically based pharmaceuticals.

In order to optimize patient access to plasma protein therapies, the unique cost structure of these medicines needs to be recognized and distinguished from other pharmaceuticals in reimbursement policies by healthcare policy makers.

Generally speaking new Member States have lower treatment levels for patients affected by plasma protein deficiency disorders, which all fall into the EU definition of rare diseases (1:2000 people). Patients who are treated with plasma protein therapies in the EU are known to have at times experienced difficulties accessing proper treatment in their country of residence and have had to travel to another Member State to receive appropriate treatment.

PPTA would therefore encourage the Commission to incorporate a provision in its recommendations recognising the special case of plasma protein therapies in reimbursement policies and highlighting the importance of having appropriate treatment levels and equal patient access to these life-saving therapies across all EU Member States.