PPTA
Plasma Protein Therapeutics Association

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BY E-MAIL and COURIER

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Subject: Unacceptable and exorbitant increase of fees and workload for variations to a Plasma Master File (PMF)

Dear Madame/Sir,

PPTA is the international trade association and voluntary standard setting organisation for the world's major producers of plasma-derived therapies and their recombinant analogues. Our members provide 60 percent of the world's needs for source plasma and protein therapies. These include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat a multitude of diseases in persons with immune deficiencies and certain neurological diseases, therapies for individuals suffering from alpha-1 anti-trypsin deficiency and albumin which is used in emergency room settings to treat patients with shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these often life-saving therapies.

When the European Commission's initiative was launched in 2007 to revise 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)" PPTA member companies were specifically appreciative about the inclusion of the Plasma Master File (PMF) into the proposed guidelines on variations. PPTA member companies were hoping for a streamlined and simplified process which would result in less workload for both, industry and regulatory agencies and also with an implied and associated reduction of costs. Particularly the possibility of grouping and worksharing were considered as a big step into this direction.

With regret, we have to inform you that neither of these expectations has been realised under the new variations regulation EC/1234/2009 which came into force at the beginning of 2010. To date we have two examples where not only the workload increased significantly, but also the costs have multiplied. The PMF is attracting fees as if it is a full product license.

Case one, which was presented at a workshop held at the Paul Ehrlich Institut on 11 May 2010 describes the 2nd step procedures before and after the implementation of EC/1234/2009. The comparison of the two procedures as presented in Annex 1 demonstrate that the workload for the company and also the involved regulatory authorities significantly increased because for this step "of purely administrative nature" (Guideline on PMF and VAMF "Second Step") now each single product dossier has to be updated resulting in an increase of electronic sequences from 1 to 100. On top of that the associated costs have exploded to 740%.

Case two (Annex 2) compared two submissions of a Type II variation to a PMF. While before the implementation of EC/1234/2009 the grouping of variations in one submission was also acknowledged in the associated fees, the company has now received an invoice charging for every single variation separately, thus increasing the total costs to 400 %.

These two examples demonstrate that the Variations Regulation for the PMF have entirely missed their intended goal. In view of the immediate and serious financial and resource impact on PPTA member companies we would like to request an urgent meeting with you and your colleagues to find an immediate solution. We would also like to urge that with regard to PMF the guidelines of the variations regulations are being revised immediately and concomitantly the respective fees should urgently undergo a profound review process. It is obvious that also other variations not related to the PMF will be affected thus further exacerbating the dilemma. The current situation is not acceptable, the additional regulatory hurdles and costs could lead to significant impairments and delays, to withdrawals of licenses in small markets due to exploding costs and thus might endanger easy access of EU patients to these often life-saving therapies.

PPTA member companies fully trust that the EC and EU authorities are l living up to the promises of "A Better Regulation" and thus are willing to rapidly change those aspects of the new legislation which are now even more bureaucratic and cost attracting than before.

As a matter of urgency we request an immediate meeting with the EMA, DGSanco and the CMDh to find a solution to be implemented as soon as possible until the regulations are amended appropriately in line with the provisions of the Better Regulation Initiative.

Sincerely Yours,

Ilka von Hoegen

Dr. Ilka von Hoegen
Senior Director, Quality and Safety

Annex 1

PMF 2nd Step Procedure

Before implementation of EC/1234/2009	**After implementation of EC/1234/2009**
Notification (exceptions IT, ES, EL)	Classification as Variation Type IA_{IN} Variation implies change of product dossiers
One submission per country as identical documentation package containing: One cover letter One certificate including Annexes One expert statement One declaration of application One list of products	Approximately 100 sequences in the electronic dossiers 65 cover letters 65 application forms (including translations and proofs of payment) Additional documentation as before
Workload: Three Working days One employee	Workload: Approximately fifteen days Significantly more employees involved
Total costs approximately: **€** 13.500	Total costs approximately: **€** 100.000

Annex 2

PMF VARIATION SUBMITTED APRIL 2008, BEFORE IMPLEMENTATION OF EMA/818151/2009:

Please refer to below retrospective listing of changes according to the new variation system:

	Procedure type	
☒ **D.5 Replacement or addition of a blood/plasma collection centre within a blood establishment already included in the PMF**	IB	
☒ **D.7 Addition of a new blood establishment for the collection of blood/plasma not included in the PMF**	II	
☒ **D.9 Addition of a new blood establishment for testing of donations and/or plasma pool not included in the PMF**	II	
☒ **D.6 Deletion or change of status (operational/non-operational) of establishment(s)/centre(s) used for blood/plasma collection or in the testing of donations and plasma pools**	☐IA	☒IB[9]
☒ **D.16 Change of kit/method used to test pools (antibody or antigen or NAT test).**	II	
EMA invoice: 1 type II variation	***€34 800*** ***(current fee for type II €57 200)***	

PMF VARIATION SUBMITTED APRIL 2010:

	Procedure type		
☒ **D.5 Replacement or addition of a blood/plasma collection centre within a blood establishment already included in the PMF**	IB		€6 400
☒ **D.7 Addition of a new blood establishment for the collection of blood/plasma not included in the PMF**	II		€57 200
☒ **D.9 Addition of a new blood establishment for testing of donations and/or plasma pool not included in the PMF**	II		€57 200
☒ **D.14 Addition of a CE-marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit**	☒IA	☐ IB[9]	€2 700
D.15 Addition of a non-CE marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit			
☒ a) The new test kit has not previously been approved in the PMF for any blood centre for testing of donations	II		€57 200
☒ **D.16 Change of kit/method used to test pools (antibody or antigen or NAT test).**	II		€57 200
Announced EMA invoice			**€237 900**

Withdrawal is possible according to EMA (Dr. Domingo), but the complete fee has to be paid. Dr. Domingo's advice was to apply for fee reduction at any time from now and to address this to the executive director.