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Ms. Maria Figuerola-Santos
DG Health and Consumers, Unit D3 Pharmaceuticals

European Commission

45 Avenue d'Auderghem
1049 BRUSSELS

Subject: Public Consultation Paper: Review of the Variations Regulation

Dear Ms Figuerola-Santos,

PPTA is the international trade association and standards-setting organization for the world's major producers of plasma derived products and recombinant analogues, collectively referred to as plasma protein therapies.

We appreciate the opportunity to provide our views in the public consultation on the review of the Commission Regulation (EC) No 1234/2008 to extent the scope of the regulation to purely national marketing authorisations.

Please find below PPTA's comments on the consultation items of the Public Consultation Paper.

General Comments:

The Directorate General for Health and consumers intends to consult all stakeholders on a number of items; one being the adjustment of some of the procedures with a view to focus resources of the authorities on variations with the most impact on public health. Biological medicinal products:

Biological Medicinal products:

At this point we would like to refer to earlier submissions during the consultation on the revision of Regulation (EC) No. 1234/2008. Manufacturers of biological products have requested at the time to adopt a risk based approach for biological medicinal products and to distinguish between minor and major variations, depending on the impact on quality, safety and efficacy of the final product and thus the impact on public health.

Plasma Master File:

We would respectfully like to propose to also review procedures that result from centralised procedures subsequently implemented on national level, specifically the Plasma Master File (PMF) 2nd Step procedure. The PMF 2nd step procedure, a purely administrative act after a centralized evaluation of the PMF, certainly has no impact on public health and unnecessarily binds resources of national regulatory authorities, which could be more efficiently used in areas of real impact on public health. Although some relief is provided by

worksharing procedures, the procedure remains superfluous and cumbersome for both NCAs and manufacturers. Please find our previous correspondence (DG Sanco 1105) on this issue attached.

The PMF 2nd step procedure at least for the "*inclusion of an updated/amended PMF, if the properties of the medicinal products are not affected"* should be simplified. For this case, we would consider a mere notification of the concerned competent authorities, without necessity to provide a product or PMF related sequence, as fully sufficient. Regarding the documentation we would propose to provide the product specific declaration of applicability and expert statement. However, documents that are already available for all competent authorities elsewhere (e.g. PMF certificate, evaluation report), should just be quoted by referencing, as is common practice e.g. for pharmacopoeia monographs. This referencing procedure should be possible for all changes to a PMF.

The proposed adaption would require minor efforts, namely marginal updating of two regulatory documents (2nd step guideline, Guidelines on the details of the various categories of variations Regulation (EC) No 1234/2008Article 4(1)(a)). A concrete proposal is reflected in the attached guideline excerpts, which would lead to a significant simplification for the industry as well as for the authorities without any loss of relevant information.

PPTA member companies are willing to pay a fee comparable to the fee for a type IA_{IN} variation for this simplified procedure to avoid any financial disincentives for the NCAs, despite the fact that the notification procedure prior to EC/1234/2008 was free of charge.

Disharmonisation between EU Member States:

Plasma derived medicinal products are manufactured from human plasma donated by volunteers, who may be compensated for their effort and time. According to the CHMP Position Statement on Non-remunerated and remunerated donors: Safety and supply of plasma derived medicinal products (EMEA/CPMP/BWP/1818/02, 30 May 2002) both non-remunerated and remunerated donors contribute to the supply with safe plasma derived medicinal products. Some countries disagree with the compensation of plasma donors and implement unfavourable regulatory provisions for plasma-derived medicinal products in national, DC and MR procedures. We believe that such practices are not in the interest of patients and a threat to public health in terms of availability of these often life-saving therapies. These practices are also against the principles of free trade among the EU Member States.

General recommendation:

We would suggest that the EU implements a system such as key performance indicators covering all procedures reviewed on a regular basis to oversee adherence of EU Member States, to avoid situations as described above and ensure that EU requirements and time lines are kept.

Consultation item no.1:

Do you agree that where dossiers are not harmonised difficulties could raise for worksharing when accepting the assessment carried out by one member state by other member states?

When dossiers are not harmonised it can be expected that difficulties do arise in a worksharing procedure, the significance of disharmonised approaches may depend on the nature and the severity of the change. Nevertheless, the option of the worksharing procedure

is an opportunity for MAHs to reduce workload and time. The provision of worksharing contributes to further increase common understanding among EU Member States.

Consultation item no. 2:

Which option a) or b) mentioned above do you consider that should be adopted to allow worksharing?

We would prefer option b), because many variations relate to very specific changes, for example quality control procedures, where scientific rationale should apply. A harmonisation of all national dossiers would be a cumbersome and time consuming procedure, where the different views of all EU member states would have to be accommodated. We do not believe that this is a feasible approach.

As stated above in the case that already harmonised dossier sections are affected by a change these variations should be allowed to undergo the worksharing procedure. The wording of Option b) should be amended to:

"b) No additional restrictions to include variations to purely national marketing authorisations as long as the worksharing variations refer to a part of the dossiers that is considered not to need harmonisation or to a part of the dossier that has already been harmonised e.g. Module 3.".

Consultation item no. 3:

Do you agree with the principle that the deadline for adoption of Commission Decisions amending marketing authorisations must be driven by public health considerations?

We agree with the principle, but the definition of public health considerations may vary among EU Member States. A classification of variations depending on their implication on public health would be helpful to provide a common understanding on what constitutes a threat to public health.

Consultation item no. 4:

Which category of variations do you consider that should be adopted within shorter deadlines?

PPTA believes that the following categories should be adopted within shorter deadlines:

- Reinforcement of the Quality Control (QC) with no impact on the product (e.g. addition of test methods, specification parameters and/or limits, in-process tests and/or limits, etc.)
- A change to a reagent (biological and non-biological).
- Minor Variation to the Finished Product with no impact on the quality, safety and efficacy of the product. ok see comment above

Consultation item no. 5:

Do you agree to extend the current system that allows holders to implement certain variations prior to the adoption of the Commission Decision (to the exclusion of those changes with most impact for public health)?

We strongly agree with this proposal. Plasma protein therapies are mostly life-saving medicinal products and sometimes in short supply. Time consuming regulatory approval

procedures for changes with no impact on the quality, safety and efficacy of plasma protein therapies may endanger the life of patients in need of these treatments.

Consultation item no. 6:

Do you consider appropriate to introduce a deadline for the implementation of changes to product information significant from a public health standpoint?

A manufacturer of a medicinal product is legally obliged to ensure that all product information is accurate. Any new information related to public health or the safety and/or efficacy of the medicinal product needs to be provided to patients and physicians as quickly as possible. Therefore, we do not see a need to introduce a deadline for implementation.

In line with the above we would also like to propose to change the Classification Guideline to a Variation Type IA when new side effects, contraindications and interactions with other substances need to be introduced into the SmPC and the package leaflet to ensure that patients and physicians are informed about important safety information as soon as possible.

Consultation item no. 7:

Do you agree with the above analysis?

The analysis is correct. The regulatory procedure to introduce small changes into the product specific information should be not more that a Type IA variation.

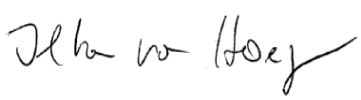
Consultation item no. 8:

Do you consider appropriate to extend the time limits for assessment of complex grouped applications to enable a larger amount of cases where grouping under one single application could be agreed by the competent authority?

We welcome the possibility to group a larger amount of cases under a single application. We agree that the timelines should be defined according to the size of the grouped application. We would not support a “one size fits all” approach, where smaller applications are subject to the same timelines as complex applications. While a general framework giving shortest and maximum review time would be helpful, we would suggest that the NCA and the MAH agree beforehand on the specific timeframe for a grouped application to allow that both parties plan for the resources needed for the review process. The current system for Type II variations already offers flexibility. This flexibility should also be extended to Type IB variations.

We hope that you will find our comments constructive and remain at your disposal for further discussion.

Yours sincerely,



Dr. Ilka von Hoegen
Senior Director, Quality and Safety

Attachments:

- DGSanco 11005

- Proposed update for 2nd step guideline

- Proposed update for Guidelines on the details of the various categories of variations Regulation (EC) No 1234/2008Article 4(1)(a))