PPTA
Plasma Protein Therapeutics Association

9 January 2013 **BY E-MAIL**
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European Commission
Directorate General for Health and
Consumers (SANCO)
B-1049 BRUSSELS

SUBJECT: "BLACK SYMBOL" IDENTIFYING MEDICINAL PRODUCTS FOR HUMAN USE THAT ARE SUBJECT TO ADDITIONAL MONITORING: PUBLIC CONSULTATION ON PHASING-IN REQUIREMENTS

Dear Madam/Sir,

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. The therapies are used in the treatment of a number of rare diseases. The diseases are often genetic, chronic, life threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. The therapies include clotting factor therapies for individuals with hemophilia A and B and other bleeding disorders; immunoglobulins to treat a complex of diseases in individuals with immune deficiencies; therapies for individuals who have alpha-1 anti-trypsin deficiency, and albumin, which is used in emergency-room settings to treat individuals with shock, trauma, burns, and other conditions.

PPTA welcomes the opportunity to comment on lead-times to introduce the black triangle in the labeling of medicinal products that are subject to additional monitoring. As a general comment we would like to point out that for biological medicinal products, such as the plasma protein therapies PPTA members manufacture, the complexity of managing the supply chain must be taken into account when timeframes are defined.

Consultation item No 1: Please comment on the time needed for the preparation and printing of the updated product information. How many weeks would be appropriate?

Basically a transition period of at least 18 months from regulatory approval of the change is required in order to introduce the revised product packaging into the local supply chain.

Product labeling:

A) Internal approval of new labeling: The updated product information needs to be approved by the relevant internal functions.

B) Change request: This starts with the Initiation of Labeling Change Request (LCR) and ends typically with the new packaging material on hand at Packaging Plant. The time for this is individually from plant to plant. A standard is somehow at least 3-4 month for a single product. However there are exceptions (product specific, logistic specific when various plants in various regions are involved in manufacturing and labeling)

Example:

- Human Albumin, 200g/l & 250g/l (licensed via MRP) (packed in plastic bags) needs 9 month lead time since facilities in Europe, US and Japan are involved in creating and implementing new labels for the plastic bag used as primary container in the manufacture of the final product. Please see below for the sequential process used for the implementation of a new label:

    1. Approval of Variation
    2. Label Development: Creation of Mock Ups in Vienna and national review by Country Regulatory Affairs in Europe
    3. signed Mock Ups are forwarded to US facility
    4. US manufacturing site creates a Labeling Change Request before implementation into the system
    5. Bag Film is ordered in Japan
    6. Bag film is shipped to US facility and available for Filling and Packaging of medicinal product

Lead time for the introduction of a new pre-printed bag (Galaxy plastic container): 5 months.

Any label change requires a new bag due to the fact that the bag (primary packaging) is pre-printed. The existing inventory will be discarded.

- Combination products: Medical device/medicinal product (label change, artwork, engineering feasibility, receiving and inspection for printing and then production planning for packaging, shipment, local release) might take up to 8 months

Advertising material:

In addition, the black triangle might be required on advertising material (e.g. MHRA). Specifications for the Black Triangle symbol can be found in the Code of Practice for the Pharmaceutical Industry as contained in the “The Association of the British Pharmaceutical Industry” (ABPI) Data Sheet Compendium. It is stated that the symbol should appear once and be located adjacent to the most prominent display of the name of the product and no written explanation of the symbol is necessary.” Advertising material of medicinal products concerned might need revision and re-printing.

Additional comments on the complexity:

C) It shall be noted that there is no information to patients or healthcare professionals on the reason why a black triangle is introduced e.g. limited efficacy data at time of initial license approval, or quality changes during life cycle of product (e.g. introduction of new or additional manufacturing site)

D) Medicinal products might be available in various presentations and strengths. This increases the complexity since every product, any strength and every presentation needs to be handled individually in the various European countries.

E) Centrally approved products might not be marketed in all EU countries or some countries might have low turn-over. Turn-over might differ significantly between EU markets. Therefore scheduling for labeling of a new product for a particular market (EU country) might take several months.

F) Shelf life impacts the timeframe how long products might be stored in the warehouse before release to the market. For biological medicinal products cold chain storage might be required.

G) If in this case a complete portfolio of products is concerned this leads to further time requirements.

H) Labeling time slots for some products / vaccines have seasonal dependencies. Please consider product specific timeframes for Influenza vaccines or TBE vaccines.

Taking into account all the various parameters, industry needs flexibility to introduce label changes in the various markets. Overall a timeframe of 18 months is needed to introduce the black triangle in the labeling of newly manufactured and packed products (please note comment below, industry anticipates extreme fallbacks in case of recall of medicinal products that are already on the market and have left the warehouse of the manufacturer).

Given the serious implications outlined above, the most practical approach would be to implement the new requirements in the context of any upcoming labeling change per already marketed product.

Consultation item No 2: How long are stocks of medicinal products packaged with the product information held by the marketing authorization holder (or the responsible manufacturer) before being released for sale and supply?

Basically the timeframe how long the stocks are being held by the marketing authorization holder depends on the turnover, shelf-life and the type of product.

1. Replenishment period: Once the new packaging material is available manufacturers have to wait until the next packaging takes place according to the manufacturing schedule. A standard timeframe would be 1 month with exceptions of up to 6 month.
2. Plant Release and Shipping: The packaging has to be released and distributed (standard: 2 weeks), the shipment has to be performed and locally received (standard 1+1 weeks) – total standard 1 month. Exceptions are complex routings such as liquid human albumin/Europe (3 month)

3. Local Release time: In some cases there is a local release / submission. In Europe this is rarely blocking inventories (exception Italy: 2 weeks), longer release times are usually in APAC (e.g. China: 3 month)
4. Local Safety Stock: The replenishment of stocks usually ensures that reserves are available in local warehouses (released) to counterbalance unexpected sales or delays in manufacturing. The amount of the reserve stock depends on the general availability of product (constrained products such as immunoglobulines less, unconstrained products such as recombinant products more) and commercial obligations (e.g. Canada, Australia, UK). A standard assumption would be 2 month.

Additional comments:

Industry needs reassurance that existing stocks of finally packed product can be used. Plasma protein therapies are manufactured from human plasma, a scarce starting material of limited availability. It is of particular importance that there is no waste of these therapies.

PPTA assumes that products released at the time the regulation is coming into effect can be distributed and stay on the market for the entire shelf life although a black symbol has to be applied according to the new pharmacovigilance provision.

By introducing the black triangle into the labeling of medicinal products under additional monitoring any danger of disrupting supply chain and shortage or not-availability of critical care, orphan and/or life-saving products shall be avoided. Appropriate transition periods are important to avoid any disruption of supply.

In conclusion, a transition period of at least 18 months from regulatory approval until introduction of new labeling (with black triangle) into the supply chain should be implemented while accepting that any product already released to the market shall not be impacted by this new requirement.

Again, from our perspective the most feasible and desired approach would be to implement the new requirements in the context of any upcoming labeling change per already marketed product.

Finally, we would like to make a general comment on the new provision. In chapter 2.1, section2 it is stated:

“Without the symbol healthcare professionals and patients may miss this information. Hence, the symbol is an important communication and awareness-rising tool”.

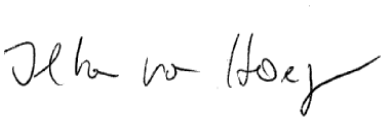
As the product information for plasma derived medicinal products always had statements in the respective safety section that the patient must be tightly monitored (see also the respective European Medicines Agency’s core monographs) and these products are used by specialized physicians generally combined with specific documentation requirements, the addition of this symbol is only generically representing a non-substantial risk minimizing measure which had been addressed under the previous regulation.

The new measure is of limited if any additional safety margin, but creates tremendous additional workload and costs for the manufacturers to update the printed packaging material. In consideration of the increasing cost pressure on health

care systems the benefit of such an additional safety measure should be carefully evaluated against the associated costs.

We hope that you will find our comments constructive and helpful. We remain at your disposal, should you have any questions or need further clarification.

Sincerely Yours,



Dr. Ilka von Hoegen
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