Plasma Protein Therapeutics Association

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PPTA Concept Paper on the Revision of the Current European Union Variation System

1. Summary

The concepts laid down in the ICH quality guidelines Q8 Pharmaceutical Development and Q9 Quality Risk Management, provide a welcome stimulus to amending the Variations Regulations[1]. The review should aim to move from the current "tick-box" concept to a risk and science based approach with common criteria and mandatory time frames for assessment and approval across Europe. A three-tiered approach, equally applicable to all medicinal products, independent of their chemical or biological nature would be the most desirable outcome of the revision process of the current variations regulations.

2. Challenges

PPTA believes that the current Variation Procedures are creating a regulatory environment in Europe that is:

- Increasing the regulatory and financial burden, consuming resources of the competent authorities, as well as Industry's, on less than critical activities.
- Inhibiting innovation and continual improvements to manufacturing processes and analytical procedures, often causing an unnecessary delay to the introduction of quality related changes beneficial to the patient in particular, and society in general.

Instead of encouraging manufacturers of medicinal products to introduce innovative technologies according to the state-of-the-art in accordance with their obligation to take account of scientific and technical progress with respect to methods of manufacture and control[2], the current requirements for variations often imposes unnecessary and cumbersome regulatory procedures. In addition, the vast majority of changes to the manufacture and control of a biological medicinal product are excluded from usage of the Type IA/IB notification submission route, and thus automatically default to a Type II variation. PPTA considers that many of the changes outlined in Annex I of the current Regulations could be processed for biological products as a notification - Type IA or IB, - with no negative implications to quality or patient safety. The reasons for certain blanket exemptions for biological and biotechnological medicinal products in Annex I to the current regulations are unclear and are in industry's view unjustified and require reappraisal as part of the Variations Regulations review. Furthermore, it is current practice with the

[1] letter from Mrs Lalis, dated 2 March 2006
[2] Article 23 of Directive 2001/83/EC, Article 16(2) of Regulation 726/2004

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authorities' that changes not listed in the variations regulations[3] require a type II variation irrespective of how minor the change might be.

Particularly for MRP variations national regulatory authorities interpret the current regulations and guidelines differently with increasing divergence from the intended goal. Also, time until approval varies significantly in the different EU Member States often causing major logistical problems for the implementation of manufacturing changes. However, this has even more serious implications for the content of the SmPC, PIL and also the new safety specification, pharmacovigilance plan and any associated risk minimisation plan, especially for matters pertaining to clinical efficacy and safety, and can lead to significantly differing information being made available to physicians and patients across the EU.

Currently there are no legally enforceable timeframes mandated for the competent authorities to amend the marketing authorisation or to issue an approval letter to the MAH following receipt of the translated SmPC/PIL/Labels, where these are required (Regulation 1084/2003 Article 6 (10)).

Plasma Protein Therapies: a specific case

Plasma-derived medicinal products are different from other medicinal products as they are manufactured from human plasma as starting material. In contrast to a well-defined chemical component, human plasma is a biological source material, which requires evolving standards and ongoing research and development efforts to ensure and improve the quality, safety and efficacy of the finished products. Consequently, the manufacturing and distribution costs of plasma-derived medicinal products are significantly higher. The costs of the starting material, human plasma, combined with expensive production costs and the unique testing and quality control including batch release constitute over 70% of the overall manufacturing costs. For chemically based pharmaceuticals the equivalent costs are typically below 15%.

In addition, in the EU and in some EEA countries plasma protein therapies are subject to the Official Control Authority Batch Release (OCABR) procedure, which requires the evaluation of individual manufacturer's batches by an Official Medicinal Control Laboratory (OMCL). This adds another layer of costs and regulatory effort to the marketing of every batch of plasma protein therapies.

Recently, the European Regulatory Authorities have implemented the Plasma Master File (PMF) system for medicinal products manufactured from human plasma. The PMF is intended to be a centrally approved stand-alone document referenced in the MA dossier for the respective medicinal products. The current regulations include no provisions to accommodate for variations to the PMF. A review of the current regulations on variations must include the development of a PMF variation system that should follow the same

[3] Commission Regulations (EC) No 1084/2003 and (EC) No 1085/2003 and the related "Guideline on dossier requirements for Type IA and IB notification (July 2003)

principles, proposed in this paper, as for variations to the MA, while respecting the specific nature of the subject of this document.

3. Key principles of a new variation system.

Any change to a regulatory system or procedure should be based on the assurance of the continued safety of patients.

A revised variations system in Europe should incorporate the following general procedural and specific quality considerations:

- Move from "tick box" concept to a **risk and science based approach**, which allows the authorities to focus their resource only on those variations that have the potential to impact safety or efficacy, or negative impact on quality and reduces the overall regulatory burden for Industry.
- Define a system which ensures **common criteria** and **mandatory time frames** for assessment and approval across Europe for centralised, MRP/DCP **and** national variations.
- Allow the single assessment of an identical change, which impacts several MAAs across different APIs, and/or different strengths and pharmaceutical forms. This should help eliminate unnecessary duplicate submissions and reviews i.e. introduces the concept of **"bulk variations"**. Bulk variations should also be possible if they concern several products irrespective whether they are licensed by different procedures (CP, MRP, or national).
- Allow the single assessment of several changes to various aspects of a single MA for simultaneous implementation **("umbrella variation")**.
- Exclude changes covered by GMP compliance and controlled by inspecting authorities.
- Post-approval submission should be based on a "regulatory agreement". This would be developed as a specific component of the MAA submission summarising the applicant's commitments for the future. Such an agreement could include such concepts as change management protocols (including comparability protocols). The regulatory agreement additionally could form the basis for measuring compliance. Submission of variations should be required only for changes that impact the "regulatory agreement".
- Any new proposal should not result in actual or perceived lowering of regulatory standards as all technical changes will still be carried out with appropriate regulatory oversight. The role of the competent authorities in protecting public safety is recognized and is not diluted in any way.
- Duplicate reviews should be eliminated. For example both EDQM and the Competent Authorities currently review changes to a Certificate of Suitability.

4. A new variation system: the three-tiered approach

PPTA respectfully proposes to replace the current system with a three-tiered approach. This approach should be equally applicable to all medicinal products, independent of their chemical or biological nature, unless a major impact on the final product can be expected:

1. **Updating - Annual reporting system**

   The use of an annual reporting system will reduce the number of regulatory submissions for administrative or minor changes and will free significant resources from the authorities and industry which can then be used to better effect. (see annex 1 for examples)

2. **Notification - "Tell and do" after 30 days**

   Submission of changes with a potential moderate impact on the final product, but evaluated by the manufacturers as being uncritical. (see annex 2 for examples)

3. **Permission - Wait for approval 3 months, maximum 60 days clock stop.**

   Should be applicable for major changes to a marketing authorisation which requires thorough assessment by the authorities prior to approval. (see annex 3 for examples)

5. Conclusion

We believe that this proposal is in line with the concepts outlined in ICH guidelines Q8 and Q9, as well as those anticipated in Q10 Quality Systems, and its implementation will enable the desired regulatory environment to become a reality. Industry's experience should be considered during the review process to ensure the most feasible and practical approaches while ensuring the safety of patients.

Annex 1: Examples

1) Annual reporting system

Change in test procedure for active substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance	
	Minor changes to an approved test procedure
Submission of a new or updated European Pharmacopoeia certificate of suitability and/or TSE certificate for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance (without requesting the underlying documentation!)	
	From a manufacturer currently approved
Change in specification of an excipient	
	Addition of a new test parameter to the specification
Tightening of specifications of an excipient, active substance, finished product not affecting the packaging material	
Change in test procedure for an excipient	
	Other changes to a test procedure, including replacement of an approved test procedure by a comparable one
Implementation of new or revised Ph.Eur. monographs or changes based on other new EU requirements	
Changes to devices or test kits that have already been certified by EU bodies	
Change in the name and/or address of a manufacturer of the active substance where no European Pharmacopoeia certificate of suitability is available	
Change in the specifications of the immediate packaging of the finished product	
	Tightening of specification limits
Change to a test procedure of the immediate packaging of the finished product	
	Minor change to an approved test procedure
Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings of ampoules change of needle shield (different plastic used)	

Change (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the dossier); spacer devices for metered dose inhalers are excluded	

Annex 2: Examples

2) Tell and do after 30 days

Change to batch release arrangements and quality control testing of the finished product	
	Replacement or addition of a site (inspected by Health Authority) where batch control/testing takes place
	Replacement or addition of a licensed manufacturer responsible for batch release
Minor change in the manufacturing process of the active substance (e.g. filter change, minimal or moderate potential to impact quality and safety)	
Validated change in batch size of active substance or intermediate	
	Up to 10-fold compared to the original batch size approved at the grant of the marketing authorization
	Downscaling
Change in the specification of an active substance or a starting material/intermediate/reagent used in the manufacturing process of the active substance	
	Addition of a new test parameter to the specification of an active substance
Change in test procedure for active substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance	
	Moderate changes to a test procedure, including replacement by a comparable test procedure or addition of a test procedure
Change in the manufacturer of the active substance or starting material/reagent/intermediate in the manufacturing process of the active substance where no European Pharmacopoeia Certificate of Suitability is available	
	Change in site of the already approved manufacturer (replacement or addition)
	Change in the manufacturer of a starting material/reagent used in manufacturing of a biological active substance

Submission of a new or updated European Pharmacopoeia certificate of suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance	
	Sterile or other substances from a new manufacturer (replacement or addition)
Replacement of an excipient with a comparable excipient	
Change in the batch size of the finished product	
	Up to10-fold compared to the original batch size approved at the grant of the marketing authorisation
	Downscaling down to 10-fold
Minor change in the manufacture of the finished product	
Change in the specification of the finished product	
	Addition of a new test parameter
Change in test procedure of the finished product	
	Moderate changes to a test procedure, including replacement by comparable test procedure or addition of a test procedure
Change in the storage conditions of the finished product or the diluted/reconstituted product on basis of pre-approved stability protocol	
Adaptation of Summary of Product Characteristics and Product Labeling to valid CoreSPC	
Addition of new suppliers of biological starting material being part of an already licensed supply organization	
Tightening of specifications of an excipient, active substance, finished product affecting the packaging material	
Consequential variation on packaging material	

Change in the name and address of the marketing authorization holder	
Change in the name of the medicinal product	
Change in name of the active substance	
Change in the name and/or address of a manufacturer of the finished product	
Change in the re-test period and/or the storage conditions of the active substance	
Change in the specifications of the immediate packaging of the finished product	
	Addition of a new test parameter
Change to a test procedure of the immediate packaging of the finished product	
	Other changes to a test procedure, including replacement or addition of a test procedure
Change in shape or dimensions of the container or closure	
Addition or replacement or deletion of a measuring or administration device not being an integrated part of the primary packaging	

Annex 3: Examples

3) Wait for approval 3 months, maximum 60 days clock stop

New manufacturer of the active substance /intermediate in the manufacturing process of the active substance where no European Pharmacopoeia certificate of suitability is available
Change in the composition of finished product without changing the applied amount of active substance and the dosage form.
Major change in the manufacturing process of active substance or finished product like omission of a manufacturing step or addition of additional processing step
Major change in the release testing of active substance and/or finished product like deletion of tests or widening of specifications or introduction of new previously unapproved technology
Major change in the specifications of a biological starting material (e.g. widening of specs, deletion of testing, less stringent selection criteria for donors)