21 October 2011

EUROPABIO CONTRIBUTION TO THE PUBLIC CONSULTATION PAPER
REVIEW OF THE VARIATIONS REGULATION (EC) No 1234/2008)

INTRODUCTION:
EuropaBio welcome the public consultation paper for review of the Variation Regulation (EC) No 1234/2008.

In addition to the EuropaBio response to the specific 9 (nine) items, EuropaBio would like to highlight some other issues in connection with the upcoming review of Regulation (EC) No 1234/2008 (due by 1st January 2012) and the introduction of the pharmacovigilance master-file in July 2012 and its impact on the EC Variation classification guideline.

However, these additional comments should not delay the extension of the scope of Regulation (EC) No 1234/2008 to nationally authorised products.

EUROPABIO RESPONSES TO THE 9 ITEMS

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?

EuropaBio response to item no. 1:
We acknowledge that non-harmonised dossiers present a potential complicating factor for the use of worksharing.

We would like to point out that specifically for product information changes it should be taken into account that the data submitted to health authorities are generally identical across EU member states. Due to divergent opinions from the national Competent Authorities or divergent national medical practices, the product information and specifically the indication section may not be fully harmonized as an outcome of national assessments. This should not prevent Marketing Authorisation Holders (MAHs) from submitting changes through the worksharing procedure and achieve harmonization of marketing authorizations progressively. A case-by-case evaluation may be necessary.

Consultation item no. 2:
Which option a) or b) mentioned above do you consider that should be adapted to allow worksharing?

EuropaBio response to item no. 2:
We recommend option b) in line with our response to item 1.

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?

EuropaBio response to item no. 3:
We agree and request that from a patient perspective this principle should cover all EU procedures including purely national procedure (CP, MRP, DCP and NP)

Consultation item no. 4:
Which category of variations do you consider should be adopted within shorter deadlines?

EuropaBio response to item no. 4:
We recommend the following principles:

Adoption of Decision:

- *Variations with significant public health implications (safety and efficacy related):*
  - *Commission Decision to be updated within 2 months of the CHMP Opinion*

- *Variations related to change of manufacturing sites, in order not to delay the issue of the CPP needed for non-EU countries:*
  - *Commission Decision to be updated within 2 months of the CHMP Opinion*

- *All other variations:*
  - *Commission Decision to be updated on a periodic basis (every 6 months)*

Implementation principles should be harmonised regardless of EU procedures (CP, MRP, DCP or NP) according to:

- *Size of public health concerns and*

- *Type II variations without labelling impact (i.e. purely CMC changes) should be implemented after a positive scientific assessment (CHMP Opinion /RMS agreement)*

Consultation item no. 5:
Do you agree to extent 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)?

EuropaBio response to item no. 5:
Yes, we support this with reference to EuropaBio response to item no. 4.

Consultation item no. 6:
Do you consider it appropriate to introduce a deadline for the implementation of changes to product information significant from a public health standpoint?

EuropaBio response to item no. 6:
We would like to highlight that it is in MAHs best interest to implement important public health related changes into their product information as quickly as possible and a specified deadline is not necessary in our view.
If needed, the definition of implementation from the EMA guidance should be consistently used across EU.

Consultation item no. 7:
Do you agree with the above analysis?

EuropaBio response to item no. 7:
We agree with the analysis that SmPCs should be more stable, i.e.:

- *Major changes addressing significant public health concerns are reflected promptly (no specific time line as MAH does it as soon as possible)*
- *Minor changes over a short period of time not addressing significant public health concerns do not need to be reflected promptly if it can be assured that CPP processes are adapted to reflect accepted variations immediately. EuropaBio suggest that those updates can be combined with major SmPC changes or can be done every 6 months as indicated under Item 1.4*

Consultation item no. 8:
Do you consider it 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?

EuropaBio response to item no. 8:
Grouping of several changes to one marketing authorisation should take place, if it facilitates the work of authorities as well as the Industry.

EuropaBio does not consider it 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. Shortest possible notification/approval times are normally the most important parameter for industry.. Currently, neither the fees structures of EMA nor national authorities incentivise grouping of Type IA and Type IB changes. Hence, administrative simplification and time lines are the most important parameters for industry.

Many changes are often submitted and introduced globally and not only for EU products.

For annual reporting the EU setup should be more in line with the US requirements, allowing the submission of an annual report within 2 months after the annual reporting date. Further, many emerging markets do not yet accept the EU annual reporting system and request immediate notifications.

*Currently, the implementation of Type IA in the EU must take place **before** submission of the variation application and some agencies even request arbitrary acceptable maximum timelines. From a global supply chain perspective, more flexibility to submit such changes sometime before implementation may be required.*

Consultation item no. 9:
Do you think that changes to the procedure in Article 21 of the Variations? Regulation is necessary?

EuropaBio response to item no. 9:
We have no specific comments

ADDITIONAL EUROPABIO COMMENTS:

These comments should not delay the extension of the scope of Regulation (EC) No 1234/2008 to nationally authorised products.

Regulation (EC) No 1234/2008 Annex I: Extension of marketing authorisation:
Regulation 1234/2008 Article 19 does not prohibit that shorter time lines can be applicable for the review of extensions of marketing authorisations. This is specifically important when combining a Type II variation (such as new indication) with an extension of a marketing authorisation (such as a new dosage form). Before the Revision of the Variation Regulation, the timeline for a type II variation had been applied by the EMA. This was a very good business practice.

EuropaBio suggest adding an introduction line to allow this option in practice:
"The following should be respected independent of the concerned EU procedure (CP, MRP/DCP or NP):
An application for an extension is normally much shorter and simpler than an application for an entire new active substance. Approval times should therefore in general be shorter in the first than in the last cases."

Regulation (EC) No 1234/2008, Annex II: Classification of variations: 2. Variations which shall be classified as major variations of Type II:
EuropaBio propose the following changes to fully implement the scientific risk based approach for Biological products:

> (e) Variations related to *major* modifications in the manufacturing process or sites of the active substance for a biological medicinal product;
>
> (f) Variations related to the introduction of a new design space or *major* extension of an approved one, where the design space has been developed in accordance with the relevant European and international scientific guidelines

If requested by the Commission, EuropaBio can offer some illustrative examples of which non- major changes can be handled as Type IA or Type IB variations.

Expected impact of the Pharmacovigilance legislations on the Variation Regulation
EuropaBio proposes that only changes to the PhV System Master File related to changes to QPPV details and changes to the location of the PhVSM will require a notification Type IA_{IN}.
A copy of the most current PhVSMF with all details will be available within 7 days of authority requests to the Marketing Authorisation Holder.

European Commission (EC) classification guideline[1]:
Based on further experience with the application of the revised classification guideline, EuropaBio suggests consideration of the following changes:

- *It should be possible to use Design Space not only for active substances (ICH Q11, still in early stage), but also for finished products (ICH Q8, final).*
- *Design Space and Post approval change management protocols should be separated.*
- *Items where biologicals (active substances and finished products) are handled more strictly than chemicals should be reviewed further, whether practical experience scientifically justifies these differentiations.*

[1] http://ec.europa.eu/health/files/betterreg/pharmacos/classification_guideline_adopted.pdf

About EuropaBio

EuropaBio's mission is to promote an innovative and dynamic biotechnology-based industry in Europe. EuropaBio, (the European Association for Bioindustries), has 62 corporate and 7 associate members operating worldwide, 2 Bioregions and 19 national biotechnology associations representing some 1800 small and medium sized enterprises.

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