Europe IFAH
Representing the European Animal Health Industry

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IFAH-Europe contribution to the Commission public consultation on the review of Variations Regulation 1234/2008

IFAH-Europe welcomes the Commission consultation to stakeholders on the review of Variations Regulation 1234/2008, and especially the invitation to address the following specific items:
(1) The extension of the scope of the Variations Regulation to purely national marketing authorisations.
(2) 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.
(3) Some workability concerns identified.
(4) Whether, in the light of the experience of last year, the procedure for the authorisation of vaccines in a pandemic setting should be amended

The Commission assessment of the situation and the 'consultation items' are repeated below, while the IFAH-Europe input is provided in text boxes and in a different character font (Arial) for easy identification.

2.1 Extension to purely national marketing authorisations

i) Change the scope: Article 1, to include in the scope of the Regulation variations to purely national marketing authorisations.

ii) Extend grouping of variations (to national MAs): Article 7, to allow single notifications or applications for several variations to purely national marketing authorisation for the same cases already envisaged in the Regulation.

iii) Include a new Chapter IV detailing the procedure for variations to purely national marketing authorisations

iv) Worksharing procedure: see consultation item 2 below.

IFAH-Europe: we fully support the extension to purely national marketing authorisations. As expressed on previous occasions in letters to the Commission and HMA[1], it will ensure that the new Regulation truly introduces simplification. Furthermore, we believe that refinements are also needed with regard to the classification of the changes. Thus, IFAH-Europe would welcome a review of the current variations classification guidelines on the basis of the acquired experience. This should considerably contribute to the decrease of the level of administrative burden by downgrading some type of variations, especially to immunological veterinary medicinal (IVMPs). Most variations to IVMPs are indeed classified as Type II, including changes to the SPC. IFAH-Europe provided proposals for classification before and during the consultation on the relevant GL – see:

IFAH_Europe_May07.pdf IFAH_Europe_May09.pdf

[1] IFAH-Europe letters to the Commission (ref. SM/mhd-0035, 04/10/2010) and to HMA (ref. RC/mhd-0034, 04/10/201 and ref. RC/mhd-014, 14/04/2011)

In July 2009, the Commission also organised a workshop to specifically address biologicals; some progress were made, though they remained limited in our views.

Here are additional examples of proposed changes to the classification:

- Vaccines registered under exceptional circumstances: in such cases, the MAH has to commit to provide stability data (up to 24 months). These data, once assessed and approved by the Rapporteur lead to a change of the shelf-life and relevant SPC update => as the data have already been assessed and approved, this should be a new Type IA (and not IB, as requested by some authorities). It could be added to C.I.3.c) as follows: "Change in shelf life on SPC, where stability data have already been evaluated and approved as part of follow-up measures".

- Deletion of a distributor => this should be a simple notification and be added as a new Type IA in the classification (to also prevent submission as Type IB, as requested by some authorities).

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?

IFAH-Europe: it is acknowledged that such difficulty could indeed arise. Nevertheless, the focus should be on harmonisation of the data package. Thus, where a Marketing Authorisation Holder (MAH) can submit one data package applicable to several marketing authorisations, this should not prevent a work-sharing procedure to be successfully carried out.

Consultation item no. 2: Which option a) or b) (below) do you consider that should be adopted to allow worksharing?

a) Not to allow worksharing where the same product has several marketing authorisations in different member states which are not harmonised. A precondition to benefit from worksharing would be the harmonisation of dossiers.

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.

IFAH-Europe: we strongly favour option b) above to best ensure that, for nationally approved products, duplication of effort from parallel evaluations is avoided and the already high administrative burden is steadily decreased. Moreover, worksharing would guarantee homogenous outcomes and identical approval timelines across all member states involved.

2.2. Focusing public resources on the procedures with most impact on public health

The managing of changes in the life of a medicinal product has traditionally required a lot of administrative resources. The Variations Regulation has simplified the procedures for marketing authorisation holders but it has lead in practice to additional workload for the Commission services. The number of variation procedures for 2011 is expected to double in comparison with 2010.

The proliferation of variation procedures is partly explained because marketing authorisation holders are not making use of the possibility to consolidate minor variations in a single annual submission that was foreseen in the Regulation in order to reduce the number of variation procedures. In fact, the current rules are being used to ensure prompt changes to summary of product characteristics also when rapid change is not justified by a public health concern. As a result thereof, some marketing authorisations are being subject to constant changes, thereby

making it more difficult for practitioners to keep track of changes with a genuine significance for public health.

IFAH-Europe: annual reporting strictly applies to Type IA notifications. For IVMPs, these variations represent a significant minority; thus and to increase the use of annual reporting, considerations should be given to downgrading Type IB to IA variations.

To address this situation the following options are being considered:

i) Deadlines for the adoption of the Commission Decision adjusted to the public health implications

At present, deadlines for the Commission to adopt Decisions range from 30 days to 6 months depending on the type of variation and procedure. In addition, all variations processed under work-sharing procedures require the adoption of a Commission Decision within 30 days, regardless of the significance thereof for public health. In contrast, safety information is at times classified as Type IB and therefore the Commission Decision may be adopted 6 months after the Opinion of the relevant committee of the European Medicines Agency.

In the interest of public health, a prompt amendment of the Summary of Product Characteristics and other Product Information should occur for variations with significant public health implications. This includes, among others, for new indications (or species in the case of veterinary medicinal products) or changes in the composition of vaccines. In addition to established categories of variations requiring prompt adoption of the relevant Commission Decision, any case identified by the Agency as critical for public health should lead to an amendment of the relevant marketing authorisation within a 2 month deadline.

Under the current system, minor variations can be implemented by the applicant without waiting for the Commission Decision to be adopted. This principle could be extended to ensure that the fact that there would be less frequent updates of the marketing authorisation would not delay the ability of concerned companies to implement the relevant changes. The right to implement the variation would be conditional upon a favourable opinion from the relevant committee of the European Medicines Agency.

In the interest of public health, crucial changes would be excluded and could only be implemented after the Commission Decision has been issued (2 months deadline).

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?

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

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)?

IFAH-Europe: all three items above relate to the deadline for adoption of a Commission Decision (CD) and are being answered all together. In principle, we agree that the deadline for adoption of CD amending marketing authorisations must be driven by public health considerations. Nevertheless, this approach must not delay the implementation of other changes that are not driven by public health considerations, but are of high importance, especially for manufacturing activities.

Also MAHs only have to wait for a CD before implementing a change in case of Type II variations to centrally authorised products (CAP) authorisations, and where the MA has to be amended. This undermines the work generated by all other variations, which MAHs can implement without CD, they include:

- All Type IB variations;
- Type II variations, including to CAPs where amendment of the marketing authorisation is not necessary (and where EMA is responsible for informing the MAH that the change can be implemented);
- Worksharing applications where EMA is not the reference authority, which applies to most cases.

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?

IFAH-Europe: from a practical point of view (manufacturing and supply chain), setting a deadline is totally inappropriate; other solutions such as information to the public/end users would be far more suitable.

ii) More stable "Summary of Product Characteristics"

The current proliferation of variation procedures has led to frequent changes to the summary of products characteristics in some cases. The Commission services aim at ensuring that changes that are required to address a significant public health concern are reflected promptly. However, the proliferation of small changes in a short period of time is considered to be detrimental as it makes more difficult to practitioners to keep up with latest information and, more fundamentally, it makes more difficult to distinguish changes with serious implications for public health from other changes.

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

IFAH-Europe: we agree with the analysis above and would support the opportunity for the applicant to decide at which point in time to group and implement minor changes to the SPC, which have no implications for public health. In addition to the difficulties frequent changes pose to the end user, they are also costly to implement at the manufacturing level. As such, any simplification of the current system would be very welcomed. As for changes impacting the labelling (other than safety concern), flexibility should be given to the applicant to implement the changes once a year for example. This will ease the stock management of the packaging elements. Therefore, we suggest managing all changes without implications for public health through annual reporting of Type IA variations.

2.3. Addressing some workability concerns identified

Article 7 foresees the possibility to group variations to the terms of the same marketing authorisation in a single application provided that the competent authority agrees to subject those variations to the same procedure. However, experience has shown that in some case the competent authority does not agree to grouping where the number and complexity of the variations does not allow performing the assessment of the application within the time limits established by the Regulation.

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?

IFAH-Europe: practice has shown that authorities can reject a grouping because it does not comply with Annex III to the Regulation, rather than for time constraints; in the end, the variations are submitted separately, but the assessments are run in parallel, thereby creating unnecessary complex procedures. Thus, we strongly question the benefit of extending the time limit for complex grouped applications.

With regard to Annex III, we recommend taking advantage of the Comitology procedure to be initiated to include the chapter on national MAs, to also amend this Annex to ensure harmonised interpretation on changes that affect the active substance and the finished product - see item 6 of Annex III that reads: "*All variations in the group relate to a project intended to improve the manufacturing process and the quality of the medicinal product concerned or its active substance(s*)". In several MRP cases, the RMS has agreed to the MAH proposal to group the changes to both the medicinal product and the active substance(s). Amending the wording of item 6 to allow such grouping would ensure predictability for industry and also competent authorities especially in mutual recognition and decentralised procedures.

Other workability aspects to address:

- Non-application of the default to Type IB concept (especially for IVMPs)

Example: variation B.II.f.1.a1 "Reduction of shelf life as packaged for sale" following out of specifications results; this should default to Type IB, whereas some authorities have asked for a Type II submission (referring to C.I.4 for 'significant changes to the SPC').

- Changes to the Detailed Description of the pharmacovigilance (PV) System (DDPS):

This applies to all authorised products, whatever the registration route. For example, a change of the QPPV details (Type IA C.I.9.b) entails the submission of changes to all marketing authorisations. Considering the high number of purely national MAs, it should be allowed to submit the updated DDPS only once to the concerned competent authorities. However, practice has shown that this is not systematically accepted by all.

Also the cost is totally disproportionate to the type of change: for instance, the cost for 10 CAPs is as follows: 1xType IA fee of €2,800 + 9 administrative fees of €540, leading to a total cost of €7,660 only to notify a change of address of the QPPV. Also taking into account that many MSs do not apply the EMA above pragmatic approach for administrative fee for each additional authorisation, the financial consequences are highly significant when a MAH can have several hundred authorisations in several countries.

Thus, we strongly recommend taking opportunity of the necessary amendment to the GL following the introduction of the master file concept as defined in Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, to also apply the concept to all MAs for VMPs as from 2012.

- Change of address affecting one or several Concerned Member States (CMSs) in a MA obtained via MRP/DCP

The GL should provide for an option to handle such administrative changes in a simple manner directly with the CMS(s) concerned and without involvement of the RMS and other CMSs, since no assessment is necessary.