Europe IFAH
Representing the European Animal Health Industry

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IFAH-Europe considerations for greater efficiency of the 'Variations Regulation' and associated guidelines

Over two years' experience with Regulation 1234/2008[1], the so-called 'Variations Regulation' has shown that the system is working fairly well. Our experience has also enabled us to identify some of its weaknesses, which we introduce herewith together with proposed solutions, and which we invite the Commission to consider as part of its currently on-going activities on Variations.

The first hurdle is the non-application of the Regulation to purely national marketing authorisations, and a major step forward will be the amendment of the Regulation to include a chapter on national marketing authorisations, whose relevant Comitology procedure is in progress. In the proposed amended Regulation[2], we noted the following amendment to Article 4: "*The Commission shall, after consulting the Member States and the Agency ~~and interested parties~~, draw up guidelines on the details of the various categories of variations...*"; the rationale behind this change would be welcomed, also IFAH-Europe believes that the guidelines review process should be well described and such description made publically available. Furthermore, we question the section at the end of the Regulation, which reads that all points in relation to purely national authorisations "*shall apply from 12 months following publication in the Official Journal*". These 12 months are rather lengthy, especially when we have been in a transition period for over two years already. Thus, only a short transition period should be introduced, where necessary.

When responding to the public consultation in October 2011[3], IFAH-Europe highlighted other aspects that create major administrative headaches; they also often generate a disproportionate cost to the maintenance of Veterinary Medicinal Products (VMPs) on the EU market, especially in relation to the pharmacovigilance system (see page 4). These hurdles are presented overleaf in more details, together with proposed changes to the classification guidelines. Finally, improvements are expected in the area of biologicals where competent authorities have not really moved away from the 'old' system of 'Default to Type II', and do not systematically apply the concept of 'Default to Type IB'; this leads to lengthy and heavy variation procedures, which are often unjustified.

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[1] Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products – *Official Journal, L 334, 12/12/2008 – p. 7*

[2] Reference: D019622/01

[3] Outcome of the Commission 2011 public consultation on Variations: http://ec.europa.eu/health/better-regulation-pc_2011_09_en.htm

Proposed changes with immediate effect and that do not require prior changes to the Commission guidelines

- **All administrative changes (e.g. change of address) affecting one or several Concerned Member States (CMSs) in a Marketing Authorisation (MA) obtained via Mutual Recognition or Decentralised Procedure (MRP/DCP)**

To notify such administrative changes, marketing authorisation holders (MAHs) are asked to submit the information to all concerned member states. This creates unnecessary burden on MAHs, and agencies who will receive information of no relevance to them. Thus, MAHs should be able to handle such changes on an individual national basis. Where CMDv refers to the CMDh Q&A[4] for such request, here is the proposed change with immediate effect:

Question 2.2: *Is it necessary to submit variation applications to all concerned member states even if they are not concerned by the specific change (e.g. change in the address of the MAH in only one CMS)?*

Answer: ~~Yes, the applications have to be submitted to all concerned member states~~ **No, any administrative change that does not concern all the CMSs and the RMS of a MRP/DCP, can be submitted to those concerned countries only.**

Improvements that require changes to the Commission 'Classification' guideline

Variation number	Description of the change	Comment	Proposed change
B.II Quality changes to the finished product			
B.II.c.3.a.2	Change in source of an excipient or reagent used in the manufacture of a biological / immunological AS or in a biological / immunological medicinal product, from TSE risk material to vegetable or synthetic origin = Type IB	In Directive 2009/9/EC, the term 'reagent' refers to laboratory reagents used for tests, and which have no contact with the product itself; in the Directive, the term 'starting material' also includes 'culture medium'. Thus, we feel it would be more appropriate to replace the term 'reagent' with 'starting material'. This way, the change could also cover, for example, the replacement of a classical culture medium by an animal component free (ACF) culture medium for the production of the active component (virus or bacterium).	Amend B.II.c.3 as follows: "Change in source of an excipient or ~~reagent~~ **starting material** with TSE risk to...' Also replace 'reagent' with 'starting material' in all relevant sub-sections of B.II.c.3.

[4] Q/A-List for the Submission of Variations according to Commission Regulation (EC) 1234/2008 - CMDh/132/2009/Rev12 of March 2012
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Variations/CMDh_132_2009_Rev12-Clean_2012_03.pdf

Variation number	Description of the change	Comment	Proposed change
B.II.d.1.a	Tightening of specifications limits of the finished product = Type IA The same applies to all the other following quality changes: - Active substance: B.I.a.4.a, B.I.b.1.a and B.I.c.2.a - Finished product: B.II.b.5.a, B.II.c.1.a and B.II.e.2.a - Medical devices: B.IV.2.a	These changes are Type IA unless condition 1 "the change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the MA application or a type II variation procedure)" is not fulfilled, in which case you would expect it to default to Type IB, though this is questionable. Also in practice, a Type II has been requested, which is totally unjustified. Thus, we suggest introducing a new variation to cover all cases where data have already been assessed and in which case a Type IA should apply.	Add a **new Type IA** variation to the classification guideline as follows: "**Implementation of changes following follow-up measures for which data have already been assessed and approved**"
B.II.f.1.b.1	Extension of the shelf life of the finished product as packaged for sale (supported by real time data) = Type IB	This variation should also take into account data that meet the requirements of the VICH guidelines.	Amend b.1 as follows: "As packaged for sale (supported by real time data **or by the extrapolation of stability data based on VICH guidelines**)"
B.III CEP/TSE/Monographs			
B.III.1.b.1 and 2	Submission of a new or updated TSE certificate, from a new or an already approved manufacturer, 1. For an active substance = Type IA_{IN} 2. For a starting material/reagent/ intermediate/or excipient = Type IA	Experience has shown that these changes can be classified as Type II by some member states, who justify the Type II by requesting an assessment of the viral safety data (in which case condition 3 is not fulfilled). This classification does not take into consideration cases where the starting material of animal origin and/or the finished product is properly inactivated and there is no viral risk; we suggest amended condition 3 to reflect such scenario.	Amend condition 3 as follows: "…for which an assessment of viral safety data is required, **unless the absence of viral risk (e.g. by inactivation) has been justified**".
C.I Safety, efficacy, pharmacovigilance changes			
C.I.2	Change in the SPC labeling or package leaflet of a generic/hybrid/biosimilar medicinal product following the assessment of the same change for the reference product a) For which no additional data are submitted = Type IB	The same should apply to changes to the SPC of an informed consent dossier, where the change has already been evaluated and approved for the reference product. In such case, a Type II has been requested in the past, whereas the generic dossier benefits from the same change (a new claim in that instance) via a Type IB 30 days procedure, which seems totally disproportionate.	Amend the variation title as follows: "Change in the SPC labeling or package leaflet of a generic/hybrid/biosimilar medicinal product **or informed consent** following the assessment of the same change for the reference product."

Variation number	Description of the change	Comment	Proposed change
C.I.8 and C.I.9	Introduction of a new PV system a) which has not been assessed by the relevant national competent authority/EMEA for another product of the same MAH = Type II b) which has been assessed by the relevant national competent authority/EMEA for another product of the same MAH (e.g. in case of MA transfer) = Type IB Changes to the pharmacovigilance system = Type IA_{IN}	The DDPS[5] is a document that describes the MAH pharmacovigilance system, i.e. it is a company, and not a product specific document. Nevertheless, MAHs currently have to submit the DDPS together with each MA application, whatever the registration route. Thus, the DDPS becomes part of all dossiers, which have to be subsequently amended when changes to the DDPS occur. For example, a change of the QPPV details (C.I.9.b) entails the submission of this change to each competent authority and for each single marketing authorisation; the latter can be facilitated by the use of the 'grouping' procedure, where accepted by all member states, which currently is not the case. This generates huge administrative burden and totally disproportionate cost for such minor administrative changes that require no assessment. For instance, the cost of a Type IA variation C.I.A.b for 10 centrally authorised products would amount to a total of €29,000 [10xType IA fee of €2,900]. This is just the cost of notifying EMA, while the same exercise has to be carried out with each national competent authority. Thus, the financial consequences are highly significant when a MAH can have several hundred authorisations across Europe. Also, in the current climate of companies' mergers and products' transfers, such changes are likely to occur even more frequently, and such cost is totally disproportionate. Thus, and pending the introduction of a legal basis for the concept of pharmacovigilance system master file, the classification must be reviewed to allow the introduction of a new system, and any changes to an existing one, to be submitted as a Type IA, where **a single Type IA notification is valid for all MAs of a same competent authority**. This notification approach will prepare the ground for the next step, i.e. the introduction of the master file concept, whereby the description of the system will be available for evaluation upon request or at inspection.	Merge C.I.8 and C.I.9 into one (and move to C.II 'Veterinary medicinal product specific changes') as follows: C.I.8: **introduction of a new system or changes to an existing system = Type IA_{IN}** ***Note: a single Type IA notification can cover all the marketing authorisations***

[5] DDPS: Detailed Description of the Pharmacovigilance System

Variation number	Description of the change	Comment	Proposed change
C.II Veterinary medicinal products – specific changes			
C.II.6	Changes to the labelling or the package leaflet, which are not connected with the summary of product characteristics = Type IB.	This currently is a Type IB for VMPs, where as it is dealt with as a notification procedure for human medicinal products; such differentiation is unjustified and a notification should apply to all products.	Amend the classification for C.II.6 to: Type IA.
Not listed			
-	Once a product has been authorised and produced for several years, the manufacturing process and/or testing procedures/specifications drift away from those described in the dossier. They are often just slight modifications to the process/testing without significant impact on the quality, safety or efficacy of the product; this nonetheless means that the processes have deviated from those described in the dossier, in which case MAHs are expected to draw an extensive list of all the changes, which is often not possible. On the other hand, the introduction of a new Type II variation to include all these changes should be considered, to ensure an appropriate assessment of the proposed changes, while removing the complexity for both authorities and industry to try and list each single change. Also the January/February 2012 CMDv press release indicates that some MSs do accept this umbreall concept for MA transfer. Thus, it should be considered for introduction in the Commission classification guideline.		Add a new Type II variation for "**Update of the quality Part 2 of the dossier with several changes, without significant impact on quality, safety or efficacy**"