

**Simplified examination of variations  
to the terms of purely national marketing authorisations?  
Yes, but first re-evaluate “old national marketing authorisations”!**

- **Response to the public consultation on the “review of Commission Regulation (EC) No 1234/2008” concerning the examination of variations to the terms of purely national marketing authorisations<sup>1</sup>.**

**Summary:**

**Prescrire is taking advantage of its contribution to a technical consultation [concerning the review of a Regulation intended to simplify the examination of purely national marketing authorisation variations] to draw the attention of the European Medicines Agency (EMA ) and of the national competent authorities to the urgent need to organise a systematic re-assessment of all old national marketing authorisations, to prevent scandals similar to the *benfluorex* (Mediator<sup>®</sup>) scandal in France from occurring in other countries of the European Union.**

Regulation (EC) No 1234/2008, adopted in 2008, enables simplified examination of variations to the terms of a marketing authorisation (MA) for medicinal products authorised through a centralised, decentralised or mutual recognition procedure.

The technical consultation pertains to revising Regulation (EC) No 1234/2008 to extend its scope to medicinal products authorised through a purely national procedure. In national MA procedures, the application is evaluated by the competent authority of one Member State (often the health products regulatory agency), and the MA only applies within that State.

## General comments

Since the inception of the European Medicines Agency (EMA) in 1995, the number of MAs granted through the centralised procedure or through mutual recognition has increased. However, 80% of MAs within the European Union are national MAs<sup>1</sup>.

**“Old national MAs”: accidents waiting to happen?** In France, *benfluorex* (Mediator<sup>®</sup>), which was responsible for a public health disaster, was authorised through an old national MA<sup>2</sup>.

Some of the purely national MAs still in force within the European Union were granted in accordance with old, disparate, national standards, dating from a time when medicines agencies did not exist. The summaries of product characteristics (SPCs) and package leaflets of medicinal products authorised through a purely national procedure are often insufficiently informative and their content

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<sup>1</sup>- European Commission Health and Consumers Directorate-General “Review of Commission Regulation (EC) No 1234/2008” Brussels, Public consultation paper; 21/09/2011. (Deadline for Public Consultation: 22 October 2011; maria-angeles.FIGUEROLA-SANTOS@ec.europa.eu)

<sup>2</sup>-The medicinal product *benfluorex* (Mediator<sup>®</sup>) was indicated as an adjuvant diabetes treatment for over 30 years, although the evidence for its efficacy was limited. In reality, this amphetamine had long been used, and extensively so, as a weight-loss drug. It took the determination of a French pulmonologist, who conducted a case-control study, for the decision to be taken to withdraw *benfluorex* (Mediator<sup>®</sup>) from the French market in 2009 and from the European Union in June 2010, and yet its extremely serious adverse effects (which were responsible for at least 500 deaths in France, particularly due to heart valve deformities) had been concealed for a very long time!

varies between countries<sup>3</sup>. The longevity of these national MAs makes these substances appear innocuous, despite the uncertainty over their safety profile<sup>4</sup>. The processes for harmonising national MAs are welcome (Article 30 of Directive 2001/83/EC), but the resources made available by the European Commission are inadequate, given the public health implications: only 10 or 12 medicinal products are subjected to the harmonisation procedure each year<sup>5</sup>. Finally, old national MAs will be introduced only gradually into paediatric harmonisation processes<sup>6</sup>.

Yet, in 2011, certain “old national MAs” (granted before the 1990s) are exposing European citizens to serious risks of harm. The Mediator° scandal should lead the EMA and the competent authorities of all Member States to take action regarding medicinal products with old national MAs (see below).

**Firstly, re-evaluate old national MAs, then harmonise the procedure for examining the remaining national MA variations.** In order to reduce the administrative burden on Medicines Agencies created by the examination of variations to national MAs, **it would be better, in parallel with the harmonisation process laid down in Article 30 of Directive 2001/83/EC, to start by scheduling a systematic re-evaluation of old MAs at national level.** This would create a virtuous circle whereby the re-evaluations would enable the withdrawal of old, unnecessary MAs from national markets, thereby reducing the quantity of remaining national MA variations to be managed.

This re-evaluation could follow the example of the process put in place by the French medicines agency (Afssaps) for MAs granted before 2005, by prioritising the medicinal products to be re-evaluated on the basis of sound criteria (products for which safety doubts exist, widely used products, etc.)<sup>7</sup>. We also propose that re-evaluations of MAs held by the same company in more than one Member State through national procedures be used to **harmonise their brand names**, favouring brand names that use the international non-proprietary name. These re-evaluations must give rise to **public assessment reports made publicly accessible on the European authorities’ websites** (EMA or Heads of Medicines Agencies (HMA)).

**Dissociate the process for issuing safety alerts from the process for evaluating variations.** Grouping variations of different types or too long delays for acceptance of a grouped variation application by the Member states concerned may delay the evaluation of these variations. To avoid delaying access to important safety information, **when a variation pertains to pharmacovigilance data, the safety warning** (stating that a certain adverse effect has been observed with a certain product under certain circumstances) **must be released without waiting for the end of the variation examination procedure.**

To improve citizens’ access to officially approved information about medicinal products, **SPCs, package leaflets and packaging mock-ups (including any dosing devices) authorised through a national procedure must also be rapidly published (for example by the end of 2012) on the EMA’s Eudrapharm database**, which should contain all the medicinal products marketed within the European Union, and **in every language of the European Union.**

Any subsequent **changes** to these documents should be **published online, along the lines of the “steps taken”**, document history that accompanies the European public assessment reports (EPARs) on the EMA website (date and nature of the change(s)). And the changes made at each variation should be highlighted, for example in bold type.

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<sup>3</sup>- One example among a great many others: the risk of prolongation of the QT interval associated with the substance *citalopram* is not mentioned in the SPC of the proprietary product Seropram°, marketed in France, yet it is mentioned in the SPC of the proprietary product Cipramil°, which is marketed in the United Kingdom.

<sup>4</sup>- For example, the French medicines agency re-evaluated several old drugs following the Mediator° scandal: it recommended the market withdrawal of *bufloxedil* and *trimetazidine*; *mequitazine* was classified as a prescription-only medicine; the use of *quinine* in cramp was re-evaluated, as was the use of *mephènesin* for self-medication (refs: *Rev Prescrire* 2011). An example at the European level: in 2011, the Heads of Medicines Agency re-evaluated *metoclopramide* and recommended that it should not be used in children (HMA “Primperan (and others) *Metoclopramide*” Rapporteur’s public paediatric assessment report; Nov 2010: 64 pages).

<sup>5</sup>- Heads of Medicines Agency - CMDh “Harmonisation of SPCs in accordance with Article 30(1) and with Article 30(2) of Directive 2001/83/EC, as amended” Article 30 Table, 17/10/2011.

<sup>6</sup>- HMA – CMDh “Article 45 of the Paediatric Regulation – EU Worksharing” Ref: CMDh/014/2008/Rev16; Sept. 2011: 13 pages.

<sup>7</sup>- Afssaps “Méthode de « priorisation » de la réévaluation du rapport bénéfices-risques des médicaments ayant une autorisation de mise sur le marché antérieure à 2005” Point d’information, July 2011: 3 pages.

## Responses to the specific questions asked in the frame of the consultation

### 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?**

Yes.

### Consultation item no. 2:

**Which option a)<sup>8</sup> or b)<sup>9</sup> mentioned above do you consider that should be adopted to allow worksharing?**

Option a) seems a better way to foster comprehensive harmonisation.

### 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?**

Yes, if the criteria that define a public health priority are safety, prevention of medical errors, and indication restrictions for safety reasons. A new indication for a “me-too” product that does not constitute a therapeutic advance should not be considered a public health priority.

To avoid delaying access to important safety information, when a proposed variation pertains to pharmacovigilance data, the safety warning (stating that a certain adverse effect has been observed with a certain product under certain circumstances) must be released without waiting for the end of the examination procedure for the proposed variations.

### Consultation item no. 4:

**Which category of variations do you consider that should be adopted within shorter deadlines?**

The following categories of variation should be adopted within shorter deadlines:

- safety information;
- information that would prevent medical errors;
- major variations, especially when they impact public health (type II).

### 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)?**

Yes, we agree for type IA variations (administrative variations).

We do not agree for variations that have a public health impact (clinical data, safety, convenience of use (packaging), useful information updates for health professionals and patients in the Summary of Product Characteristics (SPC) and package leaflet).

### 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?**

Yes, but it should not preclude the European Medicines Agency from continuing to make publicly available online the draft SPC and package leaflet that were submitted to the European Commission for approval as part of the variation application. The publishing of the drafts is in fact very welcome to accelerate access to important information.

### Consultation item no. 7:

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<sup>8</sup> - “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.”

<sup>9</sup> - “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.”

**Do you agree with the above analysis [More stable "Summary of Product Characteristics"]<sup>10</sup>?**

Yes. Pharmaceutical companies should moreover be obliged to consolidate minor variations in a single annual submission, in order to reduce the number of variation procedures.

To improve citizens' access to officially approved information about medicinal products, SPCs, package leaflets and packaging mock-ups (including any dosing devices) authorised through a national procedure must also be published online on the EMA's Eudrapharm database, which should contain all the medicinal products marketed within the European Union, and in every language of the European Union.

Any subsequent changes to these documents should be published online, along the lines of the "steps taken", document history that accompanies the European public assessment reports (EPARs) on the EMA website (date and nature of the change(s)). And the changes made at each variation should be highlighted, for example in bold type.

**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?**

No, we do not agree to extend the time limits for assessment of complex grouped applications, because it might delay the release of safety information or of information intended to prevent medical errors. Grouped applications should not be complex (need to amend Article 7 of the Regulation and/or annex III of the Regulation).

**Consultation item no. 9:**

**Do you think that changes to the procedure in Article 21 [human influenza pandemic] of the Variations Regulation are necessary?**

No comment.



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<sup>10</sup>. "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."