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AESGP Position Paper on the review of Commission Regulation (EC) No 1234/2008

AESGP is pleased to participate to this consultation on the review of Commission Regulation (EC) No 1234/2008.

Currently the implementation of the revised Variations Regulation to national authorisations varies significantly across the EU member states: some member states voluntarily implemented the new Regulation from 1 January 2010 (sometimes with minimal advance notice); others have implemented in the intervening period since then; whilst other member states have indicated that they will not implement at a national level until there is a mandatory date for implementation. This has created a very complex regulatory environment for European/global companies to manage variations. We would like to recall that the European variation system was revised in light with the 'better regulation principles' and with the main objective to come to a harmonised European system in a timely manner.

We also wonder why the draft chapter on purely national variations, which was circulated as part of the consultation document in October 2007, was not provided again as basis for the current consultation. This would have facilitated the present consultation.

Besides comments on the consultation items, we would like to understand whether the proposed review of the Regulation will be followed by a review of the classification of variations as set out in Article 26, especially in light of the implementation of the new Pharmacovigilance legislation (e.g. replacement of the DDPS by a Pharmacovigilance master file).

We also think it would be beneficial for the Commission to organise a workshop with key stakeholders to discuss feedback from this consultation.

Consultation item 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, in principle, however this should not limit the use of the worksharing (WS) procedure. We would agree that a minimum level of harmonisation may facilitate the handling of worksharing for both assessors and applicant. **However we would not agree that a pre-condition to benefit from worksharing would be the full harmonisation of dossier**. For example:

1. If the CTD section(s) that is (are) in the scope of the variation has (have) been harmonised by the MAH in the Member States (MS) that will be part of the WS procedure, it should therefore be less difficult to coordinate and accept the WS variation assessment.

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For example, a MAH could still ask for a WS-variation procedure for quality changes, even where the Quality dossier is not fully harmonised, as long as the non-harmonised topics do not influence the application and assessment of the proposed change. Such non-harmonised topics may be alternative manufacturing (packaging), control or release sites, country-specific product imprints, or in general the drug product part of the dossier where a drug substance change requires no drug-product specific data to be reviewed.

This would facilitate companies' implementation of these changes if approved in a coordinated manner which could favour better quality compliance from pharmaceutical companies.

2. A nationally approved product which has a harmonised core SmPC following Article 31 referral may be appropriate for worksharing where proposed variations affect the core SmPC, even when the product dossiers are not fully harmonised.

3. WS-variation for national non-harmonised products could still be feasible for certain variations non-dependant of CTD modules 2-5, e.g.:
   - DDPS change if the DDPS has been previously approved by the various Member States for that medicinal product nationally or for a different medicinal product from the same company
   - MAH name change or address
   - Active substance or ATC changes

4. If a new stability study data support a particular shelf-life, the previous (different) shelf-lives are of limited relevance. Similarly, most variations impacting the product information (PI) usually apply to a certain section or paragraph of the PI, therefore a prior full harmonisation of the PI is not necessary.

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

Firstly, we would like to remind of the Commission Consultation Paper dated 24 October 2007 which states as Key Item 1 the inclusion of purely national authorisations within the scope of the revised Variations legislative framework, so that "*all authorised medicinal products would be subject to the same rules for the approval and administrative handling of changes, regardless of the procedures,...*".
Hence, as a matter of principle **we agree to option b),** "***no additional restrictions to include variations to purely national marketing authorisations***".

In addition, we suggest the addition of the following wording for extending the scope of Option b) in line with the response provided to Item No. 1:"***... as long as the worksharing variations refer to a part of the dossiers that is considered not to need harmonisation or this part of the dossier is essentially similar in all NCAs where the variation is filed despite the baseline dossier may not be fully harmonised."***

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, we agree. However, the background of this question in the context of the current review document is not clear as it was always stressed in the past that this approach was behind the different schedules for the different types of variations.

In addition, we have two comments:

- This question should not only refer to the deadline for adoption of Commission Decisions but also to National Competent Authorities' (NCA) decisions, since this variation regulation would now cover all procedures (centralised, MRP, DCP and national).

- We suggest the following:

    1. **A definition of 'Public Health considerations' and 'crucial changes' would be needed**.

    2. Changes driven by public health considerations should have minimal deadline, but not to the detriment of other changes such as some unexpected events (e.g. an interruption of the supply chain that would require a rapid approval of ad hoc changes).

    3. In addition, company business needs with major financial implications if variations approval deadlines are not met by NCA should also be duly taken into account.

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

With reference to our comments in the introduction, it is proposed to reconsider the classification of various conditions together with all stakeholders (including industry representatives) aiming at re-assessing their relevance to a product's safety. Whereas the majority will likely remain unchanged regarding their classification, there will be some for which the safety relevance may be challenged.

A **better definition of changes** that could benefit from shorter approval timelines would be needed.

Classify more variations as do and tell Type IAin variations: this approach would allow for greater flexibility for the MAH to implement certain changes and may therefore decrease compliance risks. This might add flexibility to MAHs and facilitate the current situation where IA or IB approval timelines by most NCAs are much longer in practice than regulated in theory due to the huge workload variations represent to NCAs.

Changes that should be either approved within shorter timelines or fall within "Do & Tell" could be the following:
- All CMC variations, also with impact on product information → shorter timeline
- Any formal, non-content-related changes to product information texts e.g., numbering, headings, table formats → do and tell

- Unexpected supply events such as e.g. interruption of the supply chain that will require a rapid approval of ad hoc changes → Shorter approval deadlines should be possible.
- New indications & new contra-indication → shorter timeline with Commission decision prior to implementation
- Safety changes → Shorter approval deadlines should be feasible by NCAs. For example, Type IB variations needed to implement the Core Safety Profile subsequent to a WS-PSUR or the conclusions from an Article 45 of the Paediatric Regulation into each MS's language take much longer than the theoretical Type IB variation deadlines.
- Changes that do not impact the product quality, efficacy and safety, e.g. minor SPC or PL or other packaging text changes → Do & Tell pathway should be possible (e.g. implementation of a new batch releaser in the PIL or a change in the SPC or PIL or packaging that may have been already approved for a similar medicine).

Consultation item no. 5 - "Do you agree to extend 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)?"

We find fundamental for applicants to be able to plan the potential implementation of one or several given changes. Furthermore, we have the following two comments in this regard:

1. This question should not only refer to deadlines for adoption of a Commission Decision but also to a NCA's decision, since this variation regulation not only covers centrally approved medicines but also MRP/DCP medicinal products and will also cover nationally-approved medicinal products.

2. We agree with this proposal provided that:
    - Clarity is provided for changes with most impact for public health, and
    - A better definition of changes that could benefit from applying the decision without waiting for the Commission Decision or NCA decision is added.
    - The possibility to implement safety relevant changes to the product information should be provided
    - The EMA promptly makes the revised product information publically available on their website following the committee opinion. This is necessary to avoid confusing patients and healthcare professionals who may receive or access revised product information from the MAH or other sources, such as medicines compendia.

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?"

As the term "public heath" is still to be defined there will be continuously different points of view on the relevance of a change for public health. In line with the above responses # 3-5, there should be a definition of the significance of a change from a safety or compliance viewpoint.

We agree that public health is of high importance but would foresee some potential hurdles for marketing authorisation holders to meet fixed deadlines to implement changes to product

information, in case of an ongoing renewal or referral for instance. In other words, definition of fixed implementation deadlines could be pretty cumbersome for MAHs to apply and therefore they may lead to an increase of incompliance issues, due to the higher number of overlapping changes (mostly, in SPC, PIL, other labelling components or in module 3). In this regard, MAHs have either SOPs that regulate changes implementation or could agree the implementation date for a particular change with the NCA before filing the corresponding variation.

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

Yes. The situation is very much a consequence of increasing authorities' demands with respect to pharmacovigilance submissions, the paediatric regulation etc. In addition, it must be noted that too many changes have to be applied for as type II variations, the long assessment times making it impossible to provide current SmPC texts.

To avoid the proliferation of small changes in a short period of time options for grouping of non-consequential label variations should be extended to allow a consolidated implementation.

There is currently no discrimination of changes to SmPC/PIL texts with regard to relevance. National legislation and supervision of medicinal products may allow some flexibility in the implementation of a change; in most countries there is however no flexibility foreseen in the legislation. Some type of catalogue of issues which allow flexible handling would be appreciated.

One key issue for the fact that variations type IA are not more frequently grouped seems to be that the persons responsible for releasing the product to the market are concerned about consequences of problems arising later when the group is assessed. Accordingly, they prefer a "conservative approach" of several type 1A filings and waiting for their outcome rather than groupings, all the more so since they are concerned about personal liability issues. This "conservative approach" could also be an issue when considering the extension to other variations. Accordingly, it is recommended to discuss this problem not only as a MA issue but also as a manufacturing/batch release issue. Finding together pragmatic and legally founded solutions to those concerns will be beneficial to the system and will likely improve acceptance.

The new variation regulation should also ease the implementation of changes by MAHs to minimise incompliance risks. For example: by grouping the implementation of several changes that may have happened within a short time period (e.g. occurred within 6 months) in one step. This would help MAHs not only to duly inform HCPs in a more rational manner (by highlighting the changes with serious implications for public health from other changes) but also would help MAHs to minimise compliance issues when managing the implementation of so many changes at a global production level; for example, multiple changes impacting the PIL. Particularly, nowadays that certain NCAs are focusing their safety inspections on verifying that the PILs do comply with the latest changes that may have been approved.

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, as a general principle. The advantage given to Member State (MS) and MAH by grouping variations should not be jeopardised by a relevant extension of timelines. Otherwise, it might not necessarily be beneficial for MAHs to use this option and would not foster the use of grouping but rather the submission of several single variations, especially if applicants cannot anticipate the timetable that would apply to a given grouping. Furthermore, we do not understand how grouping related changes pose more of a problem for review times than submitting them separately. On the contrary, well-presented grouped changes are more reviewer-friendly to handle and assess than a number of parallel, separately-submitted changes where the reviewer has to gain an overview and is faced with multiple packages of documentation with a high level of duplication. Additionally, grouping of mixed category changes allows a longer review timeframe for the lower categories, which will follow the time schedule of the highest category in the group.

However, exceptionally and on a case by case basis extended timeline could be mutually agreed by the RMS and the company.

We suggest the Commission uses the opportunity of this revision to consider further groupings to be included in annex III.

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

Rather than a response, we would have a question and would suggest exploring the possibility of making this flexible process be extended outside influenza vaccines scope to other medications able to treat epidemic /pandemic situations.

OTHER COMMENTS

Disharmony concerning variation document requirements among Member States: we realise that some NCAs (mainly Italy) still require hard copies of original signed documents (e.g., experts' statements) whereas this is not a requirement in any other MS since the eCTD implementation.
The same applies for batch recalls (in Italy) for "safety-driven" changes which cover not only Urgent Safety Restrictions but also any change in the 'safety sections' (including indications and posology) leading to a recall from this market even if it is not considered as a 'safety' change. Such practice is not noted in other Member States.

24 October 2011