EUCOPE
European Confederation of
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REVIEW OF COMMISSION REGULATION (EC) No 1234/2008

Comments of the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE, www.eucope.org) was founded to promote companies and associations active in research, development, production and distribution of pharmaceutical products and enhance their scientific, technical, economic and legal objectives. Via the German Pharmaceutical Industry Association BPI with its 270 member companies and the UK pharma association EMIG with its 140 member companies as well as via BioDeutschland with 275 highly innovative biotech companies, EUCOPE represents more than 680 member companies, many of them SMEs. In addition, many innovative companies from Sweden, UK, Bulgaria, Italy, Greece, Germany, the Netherlands and Austria are represented on the board of the association.

I. General findings

EUCOPE appreciates the efforts of the European Commission to strive for harmonized rules regarding variations. We highly welcome the opportunity to present the views of our members.

It is understood that different variation requirements throughout Europe are difficult to handle and therefore, it is appreciated to have only one well functioning variation system. With the current variation regulation the EU aimed to facilitate the system and to reduce the workload for industry and competent authorities.

However, this approach should incorporate best practice examples from the Member States. Compared with the German system there is already room for improvement and facilitation to our opinion. A lot of variations could be classified as type IA and thus be reported on an annual basis. For example, it is not clear why an updated CEP is a type IA_{IN} or why several minor quality-related variations are categorized as IB. Therefore, it would be helpful for both industry and competent authorities to review the complete catalogue in order to obtain as much as possible type IA-variations. The German system defining only major variations and new applications should further be considered in this regard.

The Commission asked whether the worksharing procedure could also be extended to the same variations to several products with purely national marketing authorizations.

Several possibilities could be envisaged:

- Not to allow worksharing where the same product has several marketing authorizations in different member states which are not harmonized. A precondition to benefit from worksharing would be the harmonization of dossiers.
- No additional restrictions to include variations to purely national marketing authorizations as long as the worksharing variations refer to a part of the dossiers that is considered not to need harmonization.

We will outline our positions first with regard to the general topics addressed in the different sections of the consultation document (II) and then comment on the specific consultation items (III).

II. Comments on general topics of the consultation sections

Comments on section 2.1:

We would like to provide the Commission with suggestions for the variation procedure of type IB and type II (see Annex). When extending the European Variation System to the purely national marketing authorizations, it has to be considered that only one competent authority is involved in the variation procedure. Therefore, the time lines for the variation procedures can be kept shorter.

Comments on section 2.2:

We would like to highlight some of the issues that are preventing MAH from submitting minor variations as a single annual submission:

- The reporting period of the current system is not fully aligned with the US annual report system. It should be possible to submit the EU annual report within 60 days of the 1-year reporting period to allow the alignment of the annual reports for the EU and the US.
- Many non-EU countries rely on EU CPP to approve variations. For several CMC variations to be filed as IA variations, prompt submission is often favored to the annual reporting to be able to get the updated EU CPP and have those variations approved in non-EU countries in due time.

Comments on section 2.2.i):

The proposals made relate only to products authorized via the centralized procedure. For MRP/DCP products, although the Variation Regulation foresees national implementation of type II variations within 2 months of the RMS positive opinion, this is not yet followed by all competent authorities and major delays can sometimes be observed to receive the updated marketing authorization. Reinforcement of this deadline by the Commission would be necessary, in particular for changes with most impact on public health, to ensure that updated information can be made available to the patients and practitioners without delay.

Improvement of the current EU variation system: Further suggestions

- With the new Commission Regulation (EC) No. 1234/2008, the submission of the 2nd Step of the Plasma Master File is handled as a type IAIN variation. The consequence is that the costs have increased 6-fold for this regulatory procedure. Even the administrative burden to submit these variations has increased enormously.

  Before the Commission Regulation (EC) 1234/2008 became effective the submission of the 2nd step of the Plasma Master File was handled as a notification in most countries of the EU with less administrative burden and less costs for the companies. The regulatory procedure should therefore be reconsidered.

- The CMDh pilot allowing the grouping of IA variations with different reference member states (RMS) is welcomed. Transposition into the guideline as a standard procedure would be appreciated.

- Administrative burdens related to the use of the worksharing procedure should be decreased: an easy and rapid process to get the worksharing numbers for MRP/DCP products would be welcomed, in particular when this worksharing procedure applies to original and duplicate applications (same RMS), in which case no reference authority appointment is needed.

- The use of one common EU application form and cover letter for MRP/DCP products would be welcomed. Current national requirements for original signed application form or translation of those documents increase the administrative burden.

- The timetable for the review of IB variations processed in worksharing procedures should be aligned to the timetable of stand-alone IB variations (30 days). The additional review time as per the current regulation (60 days) precludes the MAH from using this worksharing procedure.

- The Classification Guideline should be changed in order to classify the implementation of new side-effects, contraindications and interactions to the SmPC and the package information as IA variations. An uncomplicated implementation of these changes improves the safety of medicinal products and is of great interests for physicians and patients. Furthermore companies are able to follow their duty keeping the SmPC and patient leaflet up-to-date as fast as possible, which is also important due to liability reasons.

- We would call upon the European Commission to establish a new section (for example section 3) “Special Purely National Medicinal Product Categories” within Chapter IV of the Regulation. Within this section, an article shall rule the specific needs of purely national marketing authorizations of homeopathic medicinal product.

III. Remarks on specific Consultation 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?

We share the view that difficulties could arise, e.g. some authorities might not accept the approval from other authorities.

Two conditions need to apply to overcome these difficulties: a) good will from the authorities to accept assessments by other authorities, b) partial dossier-harmonization applies for those dossier-parts that refer to the worksharing in question (cf. also our comment to Consultation item No. 2 below).

Notwithstanding, it is the very essence of the worksharing procedure that it allows for harmonization between member states as part of the procedure. Otherwise the procedure would be of very limited benefit. In general, the same data set has been submitted to the competent authorities, however, due to divergent opinions from the national competent authorities or divergent medical practices, the product information and specifically the indication section may not be fully harmonized. But this should not prevent MAHs from submitting changes through the worksharing procedure and achieve harmonization of marketing authorizations progressively.

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

In general worksharing should allow for harmonization between member states without too many further prerequisites.

Option a) would prevent the use of worksharing for nationally approved products as the huge efforts from both the industry and competent authorities to reach harmonization in advance would not outweigh the benefit of the possibility to use of a worksharing procedure at a later stage. In addition, the mechanism to reach such harmonization is unclear. Worksharing is a tool that is currently not used very extensively by the applicants. If option a) applied, this would create additional obstacles for the applicants to apply for a worksharing procedure. Moreover, there might be cases where a harmonization is not possible (e.g. some container-types that are registered in one country are not registered in another country, due to marketing reasons).

Option b) appears the most appropriate. A list of non-acceptable variations in case the related parts of the dossiers are not harmonized could be thought of to ensure consistent use of the worksharing procedure. In particular, product information revisions due to new safety information should be allowed even if the safety information in different SmPCs is not fully harmonized.

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?

To properly answer this question in the first place a common understanding of “public Health considerations” would be needed. Hence it is important to clearly define those 'Variations with significant public health implications'. Apart from that urgent safety restrictions are already provided as a tool to speed up things where this is really needed.

In general we see the benefits of such an approach and favor the following system for type II variations:

- for variations involving the product information, implementation is possible 30 days after the CHMP opinion and once the linguistic review process is completed,
- for all other variations, implementation is possible at the time of the CHMP opinion
- Update of the Commission decision on a periodic basis (every 6 months) except for variations with significant public health implications, for which related Commission decision should be updated within 2 months of the CHMP opinion and except for revisions related to change of manufacturing sites, in order not to delay the issue of the CPP needed for non-EU countries.

Type IB variations can be implemented as of the adoption of a positive CHMP opinion, even if they are reviewed through a worksharing procedure.

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

Implementation within a shorter timeline should be allowed for all types of variations. Especially the following categories are considered and should therefore be adopted with shorter deadlines: a) safety-related variations, and b) variations where a rapid approval is vital for the continued marketability of the product (e.g. nuclear disaster in Japan 2011, approval of additional raw-material suppliers outside Japan).

The current deadline for adoption of the EC Decision (2 months) for type II variations should be maintained for 'variations with significant public health implications' to ensure that patients and practitioners have access to updated product information on the Commission website without delay.

For variations with no significant public health implications, adoption of the Commission decision within 6 months appears sufficient if implementation is allowed anytime after the CHMP opinion. However for revisions related to change of manufacturing sites, in order not to delay the issue of the CPP needed for non-EU countries, adoption of the EC decision within 2 months should be maintained.

Apart from that some of the type IAIN could be classified as IA (e.g. updated CEPs); moreover some type IB could be re-classified as type IA (e.g. change in container shape for sterile preparation) and a lot of type II-variations could be re-classified as type IB. So, the complete catalogue should be reviewed and wherever possible be down-graded. Apart from that

pharmaceutical variations related to production, for which approval needs to be received in due time to avoid out of stock situations should be downgraded.

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)?

We agree to extend the current system due to the higher predictability to assure that planned variation submissions will not be upgraded to higher variation-categories. Furthermore we suggest to also include the changes with most impact for public health as those should be communicated as quickly as possible to patients and practitioners.

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?

No, we do not consider this appropriate. Art. 24 (5) of Commission Regulation (EC) 1234/2008 reads: “By way of derogation from the first subparagraph, urgent safety restrictions and variations related to safety issues which concern MA granted in accordance with Chapter 4 or Directive 2001/82/EC or Chapter 4 of Directive 2001/83/EC shall be implemented within a time frame agreed by the holder and the competent authority of the RMS, in consultation with the other relevant authorities.” We are of the opinion that the mutually agreed time frame shall be maintained.

We would like to highlight that it is in the MAHs best interest to implement important public health related changes into their product information as quickly as possible. So a specified deadline is not necessary in our view. In practice, this is often difficult to realize especially for products that are only manufactured infrequently. The observation of the deadline in the marketing chain of the product is difficult as well.

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 it 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?

We agree that the number of variations is high, but we observe that CMC and administrative changes represent a large part of these procedures. Many changes to the SmPC are related to safety findings or requests from the competent authorities to update the information as a result of a review of follow-up measures or PSURs. Some variation procedures could be avoided if more flexibility would be given by the competent authorities on the deadline to submit those changes.

Furthermore fewer variations would be submitted if the possibilities of grouping would be extended. We also observe that since the implementation of the new variation regulation, the EMA is stricter on this point, while more grouping was allowed in the past.

Furthermore, it would in this context be very helpful for industry if the different worksharing groups (e.g. paediatric worksharing and PSUR worksharing) would jointly agree the outcome. The different worksharing procedures have led to frequent changes to the SmPC and PIL of the same products within a very short time period. The workload and costs for the different variation procedure for industry is immense.

Apart from that it must be noted that too many changes have to be applied for as type II variations, the long assessment times making it albeit impossible to provide actual SmPC texts.

Addressing some workability concerns identified.
Article 7 foresees the possibility to group variations to the terms of the same marketing authorization 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?

Every effort leading to a more effective variation system would be welcome. However, we do not consider appropriate to extend the time limits for assessment. The reason for this is that variations are submitted in order to guarantee a continuous marketability of the product. Unpredictable extensions of procedure deadlines can endanger the marketability, and are therefore not acceptable. Moreover we are of the opinion that the competent authority already can extend time limits by means of clock-stops.

It is somewhat doubtful that granting the authorities even longer assessment times is the right way. The current variation regulation already offers flexibility for the timing of the review of type II variations: if the group is considered to be too complex, a longer clock-stop may be chosen. A lot of the current complexity comes from the attitude seen at many competent authorities to fragment simple and related changes in as many variations as possible. It would be more beneficial to take advantage from currently existing systems for the assessment of changes allowing easy grouping of almost all pharmaceutical variations and submission in a type IA like procedure.

Procedure for the authorisation of human influenza vaccines in a pandemic setting

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

No experiences.

We look forward to a continued fruitful exchange with the European Commission and remain at your disposal for any questions (+32.475.902.448).

European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

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Annex

Suggestion for the time lines for a variation procedure of type IB and type II with only one national competent authority involved:

Type IB:

The procedure for a type IB variation can be shortened to 20 days.

Day 0	The competent authority starts the procedure
Day 20	If the change can be accepted, the competent authority sends a notification of the acceptance of the change to the MAH The competent authority informs the MAH, if there are deficiencies and the variation cannot be accepted,
	If the variation could not be accepted, the MAH submits the variation again.

Type II:

The procedures for a type II variation for purely national variations can be reduced to a 15-days, 40-days and a 70 day procedure:

15-day procedure

Day 0	Start of the procedure.
Day 14	Competent authority sends the preliminary assessment report and the letter of deficiency to MAH
Clock-off	10 + 10 days (10 days for MAH to prepare the responses + 10 day for the competent authority for the preparation of the final assessment report)
Day 15	Re-start of the procedure: the competent authority sends the final assessment report to MAH Competent authority approves the change (possibly with new texts) End of procedure

40-day procedure

Day 0	Start of the procedure
Day 39	Competent authority sends the preliminary assessment report and the letter of deficiency to MAH
Clock-off	60 + 60 days (60 days for MAH to prepare the responses + 60 day for the competent authority for the preparation of the final assessment report)
Day 40	Re-start of the procedure: the competent authority sends the final assessment report to MAH Competent authority approves the change (possibly with new texts) End of procedure, if there is Break-out session
Day 55	Possible Break-out session
Day 60	End of procedure: Competent authority approves the change, possibly with amended SmPC and PIL.

70-day procedure

Day 0	Start of the procedure
Day 69	Competent authority sends the preliminary assessment report and the letter of deficiency to MAH
Clock-off	90 + 60 days (90 days for MAH to prepare the responses + 60 day for the competent authority for the preparation of the final assessment report)
Day 70	Re-start of the procedure: the competent authority sends the final assessment report to MAH Competent authority approves the change (possibly with new texts) End of procedure, if there is Break-out session
Day 95	Possible Break-out session
Day 100	End of procedure: Competent authority approves the change, possibly with amended SmPC and PIL.