Draft Commission Regulation concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary products

Response from the Proprietary Association of Great Britain

1. The Proprietary Association of Great Britain, PAGB, is the UK national trade association for over the counter medicines and food supplements. We represent the major manufacturers of these products in the UK, many of whom are multinationals with experience of regulatory structures world wide. The United Kingdom is generally considered to be one of the most advanced countries in the way it regulates over the counter medicines and PAGB is strongly supportive of MHRA and EMEA roles in international regulatory affairs.

2. We are pleased to have this opportunity to consider the draft commission regulation concerning the examination of amendments to the terms of marketing authorisations for medicinal products. PAGB welcomes the Commission's proposal as a positive step towards administrative simplification and a reduction in regulatory burden. The proposal represents a real commitment to the principles of better regulation and a valuable opportunity to significantly reduce workload for industry and regulatory agencies through simplified procedures and a reduction in duplication of work. We endorse the approach taken by the Commission which reflects many elements of the pragmatic approach to variations implemented in the UK by the MHRA as part of the Better Regulation of Medicines Initiative (BROMI) and which has been shown to have considerable positive outcomes for all parties but especially industry participants who have benefited from increased speed to market and greater predictability of timelines.

3. While PAGB and its members are entirely supportive of the proposals we recognise that they will have a significant impact on EMEA, national competent authorities and industry. For example there will be repercussions for authorities' fee incomes and IT systems through the broadening of EMEA's remit and changes in ways of working. Within industry there will be a need to implement new working procedures for regulatory, manufacturing and production personnel and in some respects personnel will be asked to act in completely the opposite way to current procedures e.g. at present manufacturing plants are instructed that nothing can be changed without approval being received from the competent authority, in the future we may be asking for changes to be made on the basis that the change will be included in an annual report to a competent authority. The impact of the changes resulting from the proposals should not be underestimated and we urge the Commission, EMEA and national competent authorities to give careful and detailed consideration to how the revised regulations are to be implemented, and to include industry in those discussions.

4. Purely National Applications
   PAGB welcomes the initiatives described in the consultation as key items. In principle we support the inclusion of purely national authorisations within the scope of the revised variations legislative framework provided that the proposals do not jeopardise the progress made in the UK under BROMI. On the basis of the proposals outlined in the consultation we do not envisage that this is likely to be problematic, however in the absence of final proposals about how variations are to be classified it is difficult to be certain. We look forward to receiving further information about the classification and the

opportunity to comment on a draft guideline. We include, at Annex 1, a list of differences between the proposed and BROMI classifications.

5. ICH and Design Space
   We recognise the value of the concept of 'design space' and the regulatory flexibility that it brings. While *prima facie* the concept appears to be of most relevance to products in development we can foresee occasions where established substances may wish to take advantage of it. We welcome therefore the possibility of creating a 'design space' and of making changes to an agreed design space by Type II variation. However, we question whether some changes to an agreed design space could be made by Type 1B variation rather than Type II and request that the quality working groups give careful consideration to this during their discussions on the classification of specific variations.

6. 'Do and Tell' Procedure
   The non-prescription medicines sector submits a disproportionately large number of variation applications as products are constantly being reviewed and updated to keep them attractive and meaningful to consumers. The implementation of a 'Do and Tell' procedure has the potential to revolutionise the way the industry works and is expected to bring enormous commercial benefits in terms of increased speed to market. We attach (as Annex 2), for illustrative purposes, examples of the impact the BROMI initiative has had in the UK.

   We have some outstanding queries regarding data requirements for annual reports, which we suggest should not be any more onerous than current requirements. The Commission will be aware that at present there is inconsistency across member states about data requirements. In our view there is a need for clear guidance on the level of data required as we would wish to avoid a situation where the view taken is that companies needed to submit the maximum amount of data required by any member state in order to ensure that the individual requirements of all member states can be met. Further queries relate to how the annual reporting procedure is to be closed; specifically how competent authorities will validate that all variations included in an annual report are eligible for notification in this way, how companies will be informed of this and what sanctions may be available in cases of non-compliance. Finally we are unclear whether separate annual reports are required for each product or if a company (or family of companies) can submit a single annual report relating to all products.

7. Worksharing
   PAGB is supportive of the principle of worksharing as a mechanism for reducing the duplication of work, and for EMEA to adopt the role of co-ordinator. However in order for this to be as effective as possible member states must accept the EMEA assessment and resist the temptation to undertake a second assessment at national level. We acknowledge that Member States competent authorities are ultimately responsible for products authorised on a national basis and that the proposals may give rise to concerns about the erosion of members states autonomy, and therefore that it may be difficult to make EMEA decisions binding, but in the absence of such a mechanism there appears to be scope for inconsistency in decisions. We would also suggest that all variations receiving a positive EMEA opinion should become Type IA. We do not see the need for Type II variations to become Type IB variations rather than Type IA, or why in that event they should require 60 days assessment rather than the usual 30 days for Type IB variations assessed outside of the worksharing procedure. In our view the EMEA opinion should close the procedure and all positive variations should subsequently become Type IA. We would also welcome guidance on what happens in the event of a negative opinion and particularly about whether in that situation applicants can still submit to individual member states.

The timings for worksharing procedures are another area where we have some concerns; in our view the designation of the worksharing lead must be achieved quickly so as not to add to the timelines and we propose that a timeframe be provided where further information has been requested rather than leaving it open-ended for EMEA.

8. Type IB by default and classification of variations
   PAGB is supportive of the guideline approach to classifying variations; we see this as introducing a degree of flexibility insofar as it is easier to amend a guideline than an Annex to the Regulation. We understand that formal consultation on the classification of specific variations will take place in the future and we look forward to contributing to these discussions. We support the suggestion that the guideline will specify Type IA and Type II variations and that those which are not listed (or line extensions as detailed in Annex I to the Regulation) shall be Type IB by default. The introduction of the option of EMEA providing a scientific recommendation on the classification of unlisted variations is welcome but we suggest that rather than the proposed 60 days a timeframe of 14 days is appropriate for this to be achieved. PAGB welcomes the suggestion that EMEA scientific recommendations will result in additions / amendments to the guideline, but we would like further clarification about what, if any, appeal and/or arbitration mechanisms will be available if an applicant disagrees with an EMEA scientific recommendation.

   In addition, we urge the Commission to develop clear guidance on the conditions associated with specific variations and about when non-compliance, in a minor way, with the conditions will push a variation into a Type II procedure. We believe that consideration should be given to identifying some instances of non-compliance which are so minor as to enable the variation to remain Type IB.

9. Grouping Variations
   We welcome the option to group variations but we recognise that the area is complex and therefore that companies will need guidance to be able to obtain the maximum benefit from this initiative. For example, we understand that one procedure can include lots of changes affecting a number of marketing authorisations but that if one variation fails then the whole package will fail. This introduces an element of uncertainty for companies and as a result they may choose not to use the option. We suggest that consideration be given to the feasibility of providing advance notice to companies that elements of a grouped package of variations are not acceptable thus affording the company the opportunity to withdraw those elements rather than lose the whole package of variations.

   PAGB members were disappointed to note that the only innovative item included in Annex II is bullet point 6 (All variations in the group relate to a project intended to improve the manufacturing process and the quality of the medicinal product concerned) and that this relates only to quality. We had hoped that the option of grouping non-consequential variations would be included in the proposals.

   PAGB would welcome a broad interpretation of marketing authorisation holder such that grouping can apply to multiple changes to different products owned by different Marketing Authorisation Holders who are part of the same family of companies.

10. Specific comments on the draft regulation

    a. <u>Article 2 –Scope</u>

    PAGB seeks clarification on the scope of the proposed regulation; particularly whether it is intended to cover herbal medicines registered under the Traditional Herbal Medicines Directive, well established and homoeopathic medicines.

b. Article 3 – Definitions

'Major variation of type II': The definition as currently drafted is very negative; we would suggest redrafting to give a more positive connotation for example by amending negative impact to highly significant impact. Companies only ever seek to undertake variations that are intended, and expected, to have no effect on or improve the quality, safety or efficacy of a medicine for example through improvement of the manufacturing process. However, the complexity of such variations and their impact on the finished product make a review by the competent authority necessary.

Definition on 'Reference Member State': We appreciate the pragmatism of this definition and the possibility to choose, for the purpose of the variation, a different Reference Member State from the one chosen for the Mutual Recognition or Decentralised procedures.

The term 'economic operator' referred to in article 22 is ambiguous and is liable to be interpreted differently in different member states. Therefore we suggest adding a definition for the term.

c. Article 5 - Scientific recommendations on unforeseen variations

As stated above PAGB welcomes the possibility of obtaining a recommendation on the classification of a variation not listed in the guideline. However, the main benefit of Article 5 should be to result in an update of the guideline itself.

In our view the 60-day time period for an EMEA opinion is too long. We suggest that unless it is shortens considerably there will be little incentive for companies to use the procedure as they may as well submit a type II variation. Alternatively we suggest that 'scientific recommendations' are categorised into two categories, firstly those where real scientific input is needed which could be a 30-day procedure and those which are a simple validation of the variation classification in which case 1 week would be sufficient.

We appreciate the reference to Article 29(2) of Directive 2001/83/EC as amended (the Serious Risk to Public Health guideline) and urge the Commission to ensure that the annex to this guideline is also updated in parallel with indications of modifications which are not susceptible to have a negative impact on the quality, safety or efficacy and thus cannot constitute a 'serious risk to public health'.

d. Article 6 - Guideline listing variations

Art. 6(1)a: In addition to our earlier comments on the proposal to list variations in a separate guideline rather than an annex to the Regulation and updated following an EMEA scientific recommendation under Article 5, we also suggest that either Article 5 or 6 be modified to make this link clearer.
Art. 6(1)b: the documentation referred to here seems to be adequately addressed in Annex III. We are of the view that it is appropriate to list the documentation to be submitted in the Regulation rather than in a guidance document so as to maintain harmonisation and consistency in the requirements.

e. Article 7 - Grouping of variations

In the concept paper, the proposal to group variations which are not directly consequential seems to be very innovative. However, when looking at Annex II of the draft legal proposal, we see that very few proposals relate to the grouping of non-consequential variations (which is current practice). Item 6 ("*All variations in the group relate to a project intended to improve the manufacturing process and the quality of the medicinal product concerned*") is the only true innovative one.

The grouping of changes should be facilitated in order to reduce the workload. This applies especially to #4 (changes to SPC, labelling and package leaflet or insert) which should also include a general update and harmonisation of a range of similar products independently of PSURs or class-labelling. A new grouping should be added concerning variations made to update a dossier.

With regard to point #7 mentioning point (n) of article 8(3) of Directive 2001/83/EC as amended which refers on the qualified person for pharmacovigilance (QPV), we are of the opinion that a change of QPV should be simple type IA/notification.

f. Articles 9(2), 10(2), 13(2), 14(2), 18(2), 19(2) and 24(2) - Validation phase

For national variations, the time spent in the validation phase of an application is often substantial and a major reason for delays (sometimes several months). Therefore, to prevent this issue from arising again and defeat one of the main purposes of this proposal, it would be best to introduce an automatic 'acknowledgment system' (i.e. automatic message acknowledging receipt of the notification) which would mark the start of the timeline. Alternatively, a maximum validation timeline (of a week for example) could be inserted in the proposal. After expiration of the deadline, the notification would be deemed validated.

This proposal of a maximum validation time would also be relevant for the 'prior approval' procedure for the variations type II (Articles 10(2), 14(2) and 19(2)) and for the work-sharing procedure (article 24(2)).

g. Articles 8, 12 and 17 - Type IA - "Do and tell procedure"

We very much appreciate the introduction of the pragmatic notification procedure ('do and tell') for the type IA variations. This proposal has a huge potential impact in the non-prescription medicine sector.

h. Article 9(5), 13(5) and 18(5) - Unlisted variations: type IB versus type II

The so-called "type IB by default" approach aims to avoid a systematic type II by default. In reality, however, it may result in a case-by-case decision whether a variation which is not listed in the guideline would be a type IB unless the competent authority deems it is a type II. This introduces a level of uncertainty for companies and therefore has the effect of adding to bureaucracy because it needs an additional procedure for defining the type of the variation concerned. Having criteria to help Marketing Authorisation Holders define a Type II variation would improve predictability. In addition, given the absence of timelines, a case-by-case decision exercise could be very lengthy.

We understand that comments on the draft guideline are not requested at this point of time. However, as the following comment pertains to the general point type II/type IB and as the inconsistency may create confusion, we take the opportunity to address it here. In the introduction part of the guideline, on page 27, it is stated that '*a variation which is classified in this guideline but which does not fulfil all the necessary conditions laid down in the relevant subcategory shall be considered to be of a type II'*. This is inconsistent with Article 4 and should be modified to reflect that the variation could be either a type II or a type IB.

i. Article 10(4), 14(4), 19(4), 24(5) - Timelines

It would be good to have a timeframe for the assessment of the supplementary information received by the authority from the applicant. Otherwise, this may lead to unwanted delays.

j. Article 14 - "Prior approval" procedure for type II variations – recognition of draft decision by Member States

The text in section 5 states that within 30 days the "relevant authorities shall recognise the draft decision and inform the competent authority of the reference member state accordingly". Here again, in order to avoid unnecessary delays which may hold back the closing of the procedure, an absence of response from one CMS would mean agreement.

k. Article 16 - Coordination group and arbitration

We appreciate the proposed extension of the competence of the Coordination Group to deal with variations. In Article 16(2)(c), we would suggest adding a more explicit reference to Article 29(2) of Directive 2001/83/EC as amended and to have the CMD(h) being involved first in case of disagreement from the MAH or a CMS on the classification of the variation.

l. Article 21 - Closure of procedures

PAGB considers that the term 'forthwith' is too vague and should be replaced by a strict timeframe.

Article 21(1) - Closure of procedures for type IA variations in the national procedure
To our understanding, type IA variations are administrative variations and therefore the principles of acceptance or rejection by the competent authorities as described in Article 21(1) do not really apply. In addition, the risk of having a type IA being rejected would go against the principles and benefits of the 'do and tell' procedure itself and of an immediate implementation (cf. Article 22). In addition, the timeline of six months to close such a procedure seems excessive. A specific example of the impact could be in applying for a Certificate of a Pharmaceutical Product (CPP) for a particular change to demonstrate that the change has been approved in the EU source country. Article 21(b) suggests that a CPP could not be certain to reflect the changes in less than 6 months if the authority has not updated the specific information. It would be advisable to reduce such duration (to one month) or to include special language relating to details provided by the authority on request so as to ensure conformity before the 6 months deadline.

m. Article 23 - Extensions of Marketing Authorisations

This article states that the same procedure is used for line extensions as for the original application. It would help understand the rationale for this stance. In the non-prescription sector a situation could occur with an older ingredient where advances in drug delivery could result in areas of significant therapeutic interest could be seen to be eligible for the centralised process. Article 23 would seem to preclude this possibility.

n. Other comments:

Annexes: We recommend adding a title to Annexes II (e.g. grouping) and III (documentation required) as it was done for Annex I.

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Annex 1: Differences between classifications in Commission proposed guideline and BROMI variations pilot

Title of variation	Commission proposal	BROMI Variations Pilot	Comment
1. Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product d) Additional Distributor or Own Label Supplier		BROMI 1A	
10. Minor change in the manufacturing process of the active substance with no changes to reagents or solvents used in the process b)	1B	BROMI 1A	
17.Change in: a) The re-test period of the active substance	1B	BROMI 1A	BROMI pilot distinguishes between actives for biological and non-biological substances
20. Change in test procedure for an excipient d) Other changes to a test procedure, including replacement of an approved test procedure by a new test procedure	1B	BROMI 1A	BROMI pilot distinguishes between actives for biological and non-biological substances
26. Change in the specifications of the immediate packaging of the finished product c) Addition of a new test parameter - not a consequence of previous assessments or commitments		BROMI 1A	
27. Change to a test procedure of the immediate packaging of the finished product c) Other changes to a test procedure, including replacement or addition of a test procedure – with no consequential change to the finished product specification		BROMI 1A	
36. Change in shape or dimensions of the container or closure a) Sterile pharmaceutical forms and biological medicinal products		BROMI 1A	
42. Change in shelf life or storage conditions	1B	BROMI 1A	BROMI pilot distinguishes between actives for biological and non-biological substances

Explanatory Notes:
Variation numbers relate to the BROMI Dossier Requirements for Type 1A and Type 1B UK National Notifications (attached)

Self-Certification BROMI - Categories of notification suitable for self certification

Type IA BROMI - Categories of notification that are considered Type IB under EU legislation but may be submitted as Type IA for national authorised products providing the specified conditions and documentation requirements are met.

Type IB BROMI - Categories of notification that are considered Type IB under EU legislation but may be submitted as Type IA for national authorised products providing the specified conditions and documentation requirements are met.

NB: It is noted that the Draft detailed guideline referred to in Article 6(1)(a): conditions for classification of variations will be subject to public consultation in the future and therefore that the classification may be changed in the final proposal

Annex 2:
Quantification of impact of BROMI Pack Design and Variations Pilots for UK OTC manufacturers

Example 1:
Self-certification of changes to non-statutory information on packaging / pack design

The implementation of a self-certification scheme for pack design has speeded up time to market and acted as a stimulus to innovation for companies. On average companies implement 12 pack design changes a year (the span being between 4 and 20 per year for PAGB member companies).

The pilot scheme indicates that the time taken to prepare, process and follow up on approvals reduces by approximately a third. The average annual administration costs for PAGB members is in the region of £570,000 per annum, if costs are reduced by a third to £380,000, each company would benefit from an annual saving of around £190,000. This equates to a saving of £8.1m in administrative costs a year for the UK OTC industry.

The cost of current regulatory system to implement pack changes for PAGB member companies is £811,668 plus the loss of opportunity costs largely dependant on the delay to get to market. Under the BROMI self-certification notification scheme the cost of implementing pack changes is reduced by one third to £541,112 – a saving of £270,556

Example 2:
Variation to packaging:

A packaging change from tubes with foil seals in tuck-end cartons to tubes with no seals and glue-end cartons. To achieve this change the profile and labelling of the cartons had to be amended as well as a 6.5 of the Summary of Product Characteristics.

The BROMI variations pilot meant that the company was able to benefit from these changes more quickly and the financial saving is estimated to be around £4000. In this instance the product concerned does not generate large numbers of sales so the savings are small but would be significant if a high turnover product was involved.

Example 3:
A minor change to a label, instigated by the manufacturing plant:

This was required to introduce a high speed manufacturing line and required the label dimensions to be changed.

<u>Current regulatory system</u>
Preparation of variation and circulation of labelling for sign-off = 3 days (man hours)
Anticipated MHRA approval times = 3 months
Total time before the change can be implemented (MHRA approval, label sign off, printing and manufacturing) = 6 months
Costs per variation:

Variation Fee	£473
Artwork generation (if required)	£500
Preparation and submission of variation (£200/day)	£600

<u>Under BROMI self-certification notification scheme</u>
Preparation of variation and final sign-off activities = 2 days (man hours)
Implementation: 2 months to sign off and print labelling

Cost savings: faster distribution can have a 5-10% cost reduction so to be able to introduce this 2-3 months earlier will have a real benefit.

Costs per self certified notification:

Variation Fee	£473
Artwork generation (if required)	£500
Preparation and submission of variation (£200/day)	£400

Further savings could be realised if differential fee rates applied to variations which are self-certified notifications and those requiring assessment and/or approval

Example 4:
Implementation of changes in the indications and target groups for nicotine replacement therapy (NRT) products.

In the UK, some NRT products have been authorised through the mutual recognition procedure (MR) procedure whereby variations had to be submitted in each member state and each had the opportunity to raise questions about the proposed changes even where the change had been approved in the UK, the reference member state. The company was unable to implement the change until all member states had completed the process.

This procedure inevitably introduced significant additional complexity to the implementation of the changes particularly with respect to timing. In addition it is time and labour intensive to prepare, submit and track the progress of applications in multiple member states. The ability to self certify changes and notify competent authorities in the affected member states would represent a significant reduction in administrative burden and enable companies to implement changes almost immediately.

Summary
The principal advantage arising from the BROMI pilot has been the reduction in timings for approvals to be received. Notifications of self-certified changes are acknowledged quickly thus enabling changes to be implemented quickly. In some cases this means companies are able to feel the advantage of a beneficial supplier change quickly. Secondly the timings are clear and predictable which allows the factories and the business to plan to implement changes as efficiently as possibly so where applicable component write off costs can be avoided or reduced.

Impact of implementation of Draft Regulation proposals across EU
The implementation of the proposals would result in similar significant reductions in administrative burden for companies with products authorised in several member states. Currently a company must prepare a separate variation for each member state where the product is available. This is a significant regulatory burden involving duplication of effort and unpredictability in timings and outcome. Variation applications must be prepared and submitted, together with the appropriate fee, in each member state.