

**Communication from the Commission — Guideline on the operation of the procedures laid down in Chapters II, III and IV of Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products**

(2009/C 323/04)

## 1. INTRODUCTION

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 <sup>(1)</sup>, hereinafter ‘the variations regulation’, was published in the Official Journal on 12 December 2008. The variations regulation aims to establish a simple, clearer and more flexible legal framework for the handling of variations to marketing authorisation of medicinal products, while ensuring a high level of protection of public and animal health.

Article 4(1)(b) of the variations regulation charges the Commission with the task of drawing up guidelines on the operation of the procedures laid down in Chapters II, III and IV of that regulation as well as on the documentation to be submitted pursuant to these procedures.

Consequently, this guideline provides details on the operation of those procedures and covers the steps to follow from the submission of an application concerning the examination of variations to the terms of a marketing authorisation to the final outcome of the procedure on the application and the timeframe and procedure for competent authorities to amend, where necessary due to an approved variation, the terms of the marketing authorisation.

This guideline should facilitate the interpretation and application of the variations regulation. In case of doubt as to the applicable rules, reference should be made to the appropriate provisions of the variations regulation.

Definitions relevant to this guideline are provided in Directive 2001/82/EC, Directive 2001/83/EC, Regulation (EC) No 726/2004 as well as in the variations regulation. In addition, for the purpose of this guideline applicants belonging to the same mother company or group of companies and applicants having concluded agreements or exercising concerted practices concerning the placing on the market of the relevant medicinal product have to be taken as the same marketing authorisation holder <sup>(2)</sup>.

This guideline applies to the variations listed in Article 1(1) of the variations regulation. Where reference is made in this

guideline to the centralised procedure it applies to the handling of variations to the terms of marketing authorisations granted in accordance with Regulation (EC) No 726/2004; where reference is made to the national procedure it applies to the handling of variations to the terms of marketing authorisations granted in accordance with Directive 87/22/EEC, Articles 32 and 33 of Directive 2001/82/EC, Articles 28 and 29 of Directive 2001/83/EC, as well as to authorisations granted following a referral, as provided for in Articles 36, 37 and 38 of Directive 2001/82/EC or Articles 32, 33 and 34 of Directive 2001/83/EC, which has led to complete harmonisation. Variations to the terms of marketing authorisation granted following purely national procedures are excluded from the scope of this guideline.

Reference in this guideline to ‘Member States concerned’, in accordance with Article 2(6) of the variations regulation, means each Member State whose competent authority has granted a marketing authorisation for the medicinal products in question; reference to ‘concerned Member States’ means all Member States concerned except the reference Member State.

## 2. PROCEDURAL GUIDANCE ON THE HANDLING OF VARIATIONS

The handling of variations covers the following categories, defined in Article 2 of the variations regulation:

- Minor variations of Type IA.
- Minor variations of Type IB.
- Major variations of Type II.
- Extensions.
- Urgent safety restriction.

For each category mentioned above, guidance is provided on the submission of the variations, grouping of variations and handling of the variations to the terms of the marketing authorisation for medicinal products for human and veterinary use listed in Article 1(1) of the variations regulation.

<sup>(1)</sup> OJ L 334, 12.12.2008, p. 7.

<sup>(2)</sup> OJ C 229, 22.7.1998, p. 4.

In order to allow optimal planning, availability of resources and identification of potential procedural issues (e.g. handling of overlapping applications), marketing authorisation holders are encouraged to inform the reference Member State or the European Medicines Agency (hereinafter 'the Agency')<sup>(1)</sup> of upcoming variation applications for the following 6-12 months. In particular, it is recommended that, at least two months in advance, the marketing authorisation holders inform the reference Member State or the Agency about the submission of grouped variations which are not listed in Annex III of the variations regulation together with a justification for grouping.

The reference Member State or the Agency is available to address any questions which marketing authorisation holders may have regarding a particular upcoming variation application. Where appropriate, a pre-submission discussion may be organised with the reference Member State or the Agency in order to obtain further regulatory and procedural advice specifically addressing the upcoming application(s).

It must be noticed that where a group of variations consists of different types of variations, the group must be submitted and will be handled according to the 'highest' variation type included in the group. For instance, a group consisting of an extension and a major variation of Type II will be handled as an extension application; a group consisting of minor variations of Type IB and Type IA will be handled as a Type IB notification.

Where reference is made in this guideline to the submission of variations' notifications or applications, the number of copies to be submitted will be made public for each type of procedure by the Agency as regards the centralised procedure and by the coordination groups, established by Article 31 of Directive 2001/82/EC as regards veterinary medicinal products and Article 27 of Directive 2001/83/EC as regards medicinal products for human use (hereinafter, 'the coordination group'), as regards the national procedure.

Marketing authorisation holders are advised that, any information related to the implementation of a given variation should immediately be provided when requested by the relevant authority.

### 2.1. Minor variations of Type IA

Hereby guidance is provided on the application of Articles 7, 8, 11, 14, 17, 23 and 24 of the variations regulation to minor variations of Type IA.

The variations regulation and the 'Commission guideline on the details of the various categories of variations' (hereinafter referred to as 'the Commission Classification Guideline')

<sup>(1)</sup> Where reference is made to 'reference Member State' in this context, this applies to products approved via a national procedure. Where reference is made to the Agency, this applies to products approved via the centralised procedure.

set-out a list of changes to be considered as minor variations of Type IA. Such minor variations do not require any prior approval, but must be notified by the marketing authorisation holder within 12 months following implementation ('Do and Tell' procedure). However, certain minor variations of Type IA require immediate notification after implementation, in order to ensure the continuous supervision of the medicinal product.

The Commission Classification Guideline clarifies the conditions which must be met in order for a change to follow a Type IA notification procedure, and specifies which minor variations of Type IA must be notified immediately following implementation.

#### 2.1.1. Submission of Type IA notifications

Within 12 months or immediately after implementation of a minor variation of Type IA, the marketing authorisation holder must submit simultaneously to all Member States concerned or to the Agency a notification. It is possible for a marketing authorisation holder to include a minor variation of Type IA which is not subject to immediate notification in the submission of a minor variation of Type IA for immediate notification or with any other variation. The conditions laid down in Articles 7(2)(a) and 7(2)(b) of the variations regulation should be fulfilled.

The twelve months deadline to notify minor variations of Type IA allows an annual reporting for these variations, where a marketing authorisation holder submits several minor variations of Type IA which have been implemented the previous twelve months.

The marketing authorisation holder may group several minor variations of Type IA under a single notification, as established in Article 7(2) of the variations regulation. For doing so, the variations regulation allows various possible solutions; the holder may submit a group of minor variations of Type IA to the terms of one marketing authorisation under a single notification as long as they are notified at the same time to the same relevant authority. The marketing authorisation holder may also group several minor variations of Type IA to the terms of several marketing authorisations under a single notification provided those variations are the same for all marketing authorisations and they are notified at the same time to the same relevant authority.

Where annual reporting and grouping of minor variations of Type IA are combined, it may be the case that the so called 'annual report' includes several notifications; some of this notifications referring to single minor variations of Type IA, others referring to group of minor variations of Type IA to the terms of one marketing authorisation and others referring to group of the minor variations of Type IA to the terms of several marketing authorisation as foreseen in Article 7(2)(a) of the variations regulation.

Where conditions for grouping are not met, the annual report will include one notification for each variation submitted.

The notification must contain the elements listed in Annex IV of the variations regulation, presented as follows in accordance with the appropriate headings and numbering of 'The rules governing medicinal products in the European Community', Volume 2B, Notice to applicants (hereinafter EU-CTD) format or the Notice to applicants Volume 6B format (veterinary medicinal products when EU-CTD format is not available):

- Cover letter.
- The completed EU variation application form (published in the Notice to applicants), including the details of the marketing authorisation(s) concerned, as well as a description of all variations submitted together with their date of implementation. Where a variation is the consequence of or related to another variation, a description of the relation between these variations should be provided in the appropriate section of the application form.
- Reference to the part of the Commission Classification Guideline, indicating that all conditions and documentation requirements are met, or reference to the published Article 5 Recommendation, if applicable, used for the relevant application.
- All documentation as specified in the Commission Classification Guideline.
- In case that the variations affect the summary of product characteristics, labelling or package leaflet: the revised summary of product characteristics, labelling or package leaflet (hereinafter referred to as 'product information'), presented in the appropriate format. Where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the Type IA variation, mock-ups or specimens should be provided according to Chapter 7 of Volume 2A or 6A of the Notice to applicants or as discussed with the reference Member State or the Agency on a case-by-case basis.

For variations in the national procedure, the reference Member State should additionally receive the list of dispatch dates indicating the Type IA Variation procedure number, the dates on which the applications have been sent to each Member State concerned and confirmation that the relevant fees have been paid as required by national competent authorities.

For variations in the centralised procedure, the relevant fee for the minor variation(s) of Type IA, as provided for in Council Regulation (EC) No 297/95, should be paid in accordance with the Agency's financial procedures.

For grouped minor variations of Type IA concerning several marketing authorisations from the same holder in accordance with Article 7 of the variations regulation, a common cover

letter and application form should be submitted together with separate supportive documentation and revised product information (if applicable) for each medicinal product concerned. This will allow the relevant authorities to update the dossier of each marketing authorisation included in the group with the relevant amended or new information.

#### 2.1.2. Type IA variations review for national procedure

The reference Member State will review the Type IA notification within 30 days following receipt.

By Day 30, the reference Member State will inform the marketing authorisation holder and concerned Member States of the outcome of its review. In case the marketing authorisation requires any amendment to the decision granting the marketing authorisation, all Member States concerned will update the marketing authorisation within two months following the receipt of the outcome of the review sent by the reference Member State or within six months following the receipt of the outcome of the review sent by the reference Member State for minor variations of Type IA requiring immediate notification.

Where one or several minor variations of Type IA are submitted as part of one notification, the reference Member State will inform the marketing authorisation holder which variation(s) have been accepted or rejected following its review. The marketing authorisation holder shall immediately cease to apply the rejected variation(s). While in the case of minor variations of Type IA, failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the applicant provides any missing documentation immediately on request of the relevant authority, it should be highlighted that a minor variation of Type IA may in specific circumstances be rejected with the consequence that the applicant must cease to apply already implemented variations.

#### 2.1.3. Type IA variations review for centralised procedure

The Agency will review the Type IA notification within 30 days following receipt, without involvement of the rapporteur for the product concerned appointed by the Committee for Medicinal Products for Human Use or by the Committee for Veterinary Medicinal Products. However, a copy of the Type IA notification will be submitted by the Agency to the rapporteur for information.

By Day 30, the Agency will inform the marketing authorisation holder and the Commission of the outcome of its review, as well as whether the Commission Decision granting the marketing authorisation requires any amendments. In such case, the Commission will update the marketing authorisation within two months or within six months for minor variations of Type IA requiring immediate notification.

Where several minor variations of Type IA are submitted as part of one notification, the Agency will clearly inform the marketing authorisation holder and the Commission which variation(s) have been accepted or rejected following its review. The marketing authorisation holder shall immediately cease to apply the rejected variation(s). While in the case of minor variations of Type IA, failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the applicant provides any missing documentation immediately on request of the Agency, it should be highlighted that a minor variation of Type IA may in specific circumstances be rejected with the consequence that the applicant must cease to apply already implemented variations.

Where a group of minor variations of Type IA to the terms of one marketing authorisation have been approved, the Commission will update the marketing authorisation with one single decision to cover all the approved minor variations of Type IA.

Where a group of minor variations of Type IA to the terms of several marketing authorisations have been approved, the Commission will update the marketing authorisation with one decision per marketing authorisation concerned.

## 2.2. Minor variations of Type IB

Hereby guidance is provided on the application of Articles 7, 9, 11, 15, 17, 23 and 24 of the variations regulation to minor variations of Type IB.

The variations regulation and the Commission Classification Guideline establish which changes are to be considered as minor variations of Type IB. Such minor variations must be notified before implementation. The marketing authorisation holder must wait a period of 30 days to ensure that the notification is deemed acceptable by the relevant authorities before implementing the change ('Tell, Wait and Do' procedure).

### 2.2.1. Submission of Type IB notifications

The marketing authorisation holder must submit simultaneously to all Member States concerned, or to the Agency, a notification for minor variations of Type IB.

Marketing authorisation holders may group the submission of several minor variations of Type IB, or group the submission of a minor variation of Type IB with other minor variations, for the same marketing authorisation into one single notification, provided that this corresponds to one of the cases listed in Annex III of the variations regulation or when this has been agreed previously with the reference Member State or the Agency.

Where the same minor variation of Type IB or the same group of minor variations as stated above affect several marketing authorisations owned by the same holder, the marketing

authorisation holder may choose to submit these variations as one application for 'worksharing' (see section 3 on 'work-sharing').

The notification must contain the elements listed in Annex IV of the variations regulation, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format or the Notice to applicants Volume 6B format (veterinary medicinal products when EU-CTD format is not available):

- Cover letter.
- The completed EU variation application form (published in the Notice to applicants), including the details of the marketing authorisations(s) concerned. Where a variation is the consequence of or related to another variation, a description of the relation between these variations should be provided in the appropriate section of the application form. Where a variation is considered unclassified, a detailed justification for its submission as a Type IB notification must be included.
- Reference to the part of the Commission Classification Guideline or reference to the published Article 5 Recommendation, if applicable, used for the relevant application.
- Relevant documentation in support of the proposed variation including any documentation specified in the Commission Classification Guideline.
- For variations requested by the competent authority resulting from new data submitted e.g. pursuant to post authorisation conditions or in the framework of pharmacovigilance obligations, a copy of the request should be annexed to the cover letter.
- In case that the variations affect the summary of product characteristics, labelling or package leaflet: the revised product information presented in the appropriate format. Where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the minor variation of Type IB, mock-ups or specimens should be provided according to Chapter 7 of Volume 2A or 6A of the Notice to applicants or as discussed with the reference Member State or the Agency on a case-by-case basis.

For variations in the national procedure, the reference Member State should additionally receive the list of dispatch dates indicating the Type IB Variation procedure number, the dates on which the applications have been sent to each Member States concerned and confirmation that the relevant fees have been paid as required by national competent authorities.

For variations in the centralised procedure, the relevant fee for the minor variation(s) of Type IB, as provided for in Council Regulation (EC) No 297/95, should be paid in accordance with the Agency's financial procedures.

### 2.2.2. Type IB variations review for national procedure

Upon receipt of a Type IB notification, the notification will be handled as follows:

The reference Member State will check within seven calendar days whether the proposed change can be considered a minor variation of Type IB, and whether the notification is correct and complete ('validation') before the start of the evaluation procedure.

When the proposed variation is not considered a minor variation of Type IB following the Commission Classification Guideline or has not been classified as a minor variation of Type IB in a recommendation pursuant Article 5 of the variations regulation, and the reference Member State is of the opinion that it may have a significant impact on the quality, safety or efficacy of the medicinal product, the reference Member State will inform the concerned Member States and the marketing authorisation holder immediately.

If the concerned Member States do not disagree within further seven calendar days, the marketing authorisation holder will be requested to revise and supplement its variation application so that the requirements for a major variation of Type II application are met. Following receipt of the valid revised variation application, a Type II assessment procedure will be initiated (see section 2.3.2).

If the concerned Member States disagree with the reference Member State, the reference Member State shall take the final decision on the classification of the proposed variation having taken into account the comments received.

When the reference Member State is of the opinion that the proposed variation can be considered a minor variation of Type IB, the marketing authorisation holder will be informed of the outcome of the validation and of the start date of the procedure.

Within 30 days, following the acknowledgement of receipt of a valid notification, the reference Member State will notify the marketing authorisation holder of the outcome of the procedure. If the reference Member State has not sent the holder its opinion on the notification within 30 days following the acknowledgement of receipt of a valid notification, the notification shall be deemed acceptable.

In case of an unfavourable outcome, the marketing authorisation holder may amend the notification within 30 days to take due account of the grounds for the non-acceptance of the variation. If the marketing authorisation holder does not amend the notification within 30 days as requested, the variation shall be deemed rejected by all concerned Member States.

Within 30 days of receipt of the amended notification, the reference Member State will inform the marketing authorisation holder of its final acceptance or rejection (including the grounds for the unfavourable outcome) of the variation(s). Concerned Member States will be informed accordingly.

Where a group of minor variations were submitted as part of one notification, the reference Member State will inform the marketing authorisation holder and the concerned Member States which variation(s) have been accepted or rejected following its review.

Where necessary, the relevant authorities will update the marketing authorisation within six months following closure of the procedure by the reference Member State. However, the accepted minor variations of Type IB variation may be implemented without awaiting the update of the marketing authorisation.

### 2.2.3. Type IB variations review for centralised procedure

Upon receipt of a Type IB notification, the Agency will handle the notification as follows:

The Agency will check within seven calendar days whether the proposed change can be considered a minor variation of Type IB, and whether the notification is correct and complete ('validation') before the start of the evaluation procedure.

When the proposed variation is not considered a minor variation of Type IB following the Commission Classification Guideline or has not been classified as a minor variation of Type IB in a recommendation pursuant Article 5 of the variations regulation, and the Agency is of the opinion that it may have a significant impact on the quality, safety or efficacy of the medicinal product, the marketing authorisation holder will be informed accordingly and will be requested to revise and supplement its variation application so that the requirements for a major variation of Type II application are met. Following receipt of the valid revised variation application, a Type II assessment procedure will be initiated (see section 2.3.4).

When the Agency is of the opinion that the proposed variation can be considered a minor variation of Type IB, the marketing authorisation holder will be informed of the outcome of the validation and of the start date of the procedure.

The rapporteur will be involved in the review of the Type IB notification.

Within 30 days following the acknowledgement of receipt of a valid notification, the Agency will notify the marketing authorisation holder and the Commission of the outcome of the procedure. If the Agency has not sent the holder its opinion on the notification within 30 days following the acknowledgement of receipt of a valid notification, the notification shall be deemed acceptable.

In case of an unfavourable outcome, the marketing authorisation holder may amend the notification within 30 days to take due account of the grounds for the non-acceptance of the variation. If the marketing authorisation holder does not amend the notification within 30 days as requested, the notification will be rejected.

Within 30 days of receipt of the amended notification, the Agency will inform the marketing authorisation holder and the Commission of its final acceptance or rejection (including the grounds for the unfavourable outcome) of the variation(s) and whether the Commission Decision granting the marketing authorisation requires any amendments.

Where a group of minor variations are submitted as part of one notification, the Agency will clearly inform the marketing authorisation holder which variation(s) have been accepted or rejected following its review.

Where necessary, the Commission will update the marketing authorisation within six months following receipt of the Agency Notification. However, the accepted minor variation(s) of Type IB may be implemented without awaiting the six-monthly update of the marketing authorisation and the agreed change(s) should be included in the Annexes of any subsequent Regulatory Procedure.

Where a group of minor variations to the terms of one marketing authorisation submitted as part of one notification have been approved, the Commission will update the marketing authorisation with one single decision to cover all the approved minor variations.

### 2.3. Major variations of Type II

Hereby guidance is provided on the application of Articles 7, 10, 11, 13, 16, 17, 23 and 24 of the variations regulation to major variations of Type II.

The variations regulation and the Commission Classification Guideline establish which changes are to be considered as major variations of Type II. Such major variations require prior approval before implementation ('Prior authorisation' procedure).

#### 2.3.1. Submission of Type II applications

Where a major variation of Type II is made, the marketing authorisation holder must submit simultaneously to all Member States concerned, or to the Agency, an application.

Marketing authorisation holders may group the submission of several major variations of Type II, or to group the submission of major variation(s) of Type II with other minor variations, for the same marketing authorisation into one single application, provided that this corresponds to one of the cases listed in Annex III of the variations regulation or when this has been agreed with the reference Member State or the Agency.

Where the same major variation of Type II or the same group of variations as stated above affect several marketing authorisations owned by the same holder, the marketing authorisation holder may choose to submit these variations as one application for 'worksharing' (see section 3 on 'worksharing').

The application must contain the elements listed in Annex IV of the Regulation, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format or the Notice to applicants Volume 6B format (veterinary medicinal products when the EU-CTD format is not available):

- Cover letter.
- The completed EU variation application form (published in the Notice to Applicants), including the details of the marketing authorisation(s) concerned. Where a variation is the consequence of or related to another variation, a description of the relation between these variations should be provided in the appropriate section of the application form.
- Reference to the part of the Commission Classification Guideline or reference to the published Article 5 Recommendation, if applicable, used for the relevant application.
- Supporting data relating to the proposed variation(s).
- Update or Addendum to quality summaries, non-clinical overviews and clinical overviews (or expert reports for veterinary medicinal products) as relevant. When non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2.
- For variations requested by the competent authority resulting from new data submitted e.g. pursuant to post authorisation conditions or in the framework of pharmacovigilance obligations, a copy of the request should be annexed to the cover letter.
- In case that the variation affects the summary of product characteristics, labelling or package leaflet: the revised product information, presented in the appropriate format. Where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the Type II variation, mock-ups or specimens should be provided according to Chapter 7 of Volume 2A or 6A of the Notice to applicants or as discussed with the reference Member State or the Agency on a case-by-case basis.

For variations in the national procedure, the reference Member State should additionally receive the list of dispatch dates indicating the Type II Variation procedure number, the dates on which the applications have been sent to each Member State concerned and confirmation that the relevant fees have been paid as required by national competent authorities.

For variations in the centralised procedure, the relevant fee for the Type II variation(s), as provided for in Council Regulation (EC) No 297/95, should be paid in accordance with the Agency's financial procedures.

### 2.3.2. Type II variations assessment for national procedure

Upon receipt of a Type II application, the reference Member State will handle the application as follows:

If the application has been submitted simultaneously to all the Member States concerned and contains the elements listed in point 2.3.1, the reference Member State will acknowledge receipt of a valid application of a major variation of Type II. The procedure starts from the date of acknowledgement of the receipt of a valid application by the reference Member State shall start the procedure. The marketing authorisation holder and the concerned Member States will be informed of the timetable at the start of the procedure.

As a general rule, for major variations of Type II, a 60-day evaluation timetable will apply. This period may be reduced by the reference Member State having regard to the urgency of the matter, particularly for safety issues, or may be extended by the reference Member State to 90 days for variations concerning changes or additions to the therapeutic indication. For variations for veterinary medicinal products listed in Part 2 of Annex V of the variations regulation a 90-day timetable will apply.

The reference Member State will prepare a draft assessment report according to the communicated timetable and will circulate it to the concerned Member States for comments as well as to the marketing authorisation holder for information. The concerned Member States should send to the reference Member State, their comments on the draft assessment within the timeline as stated in the timetable.

Within the evaluation period, the reference Member State may request the marketing authorisation holder to provide supplementary information.

The procedure will be suspended until the receipt of the supplementary information. As a general rule, a suspension of one month will apply. For longer suspension the marketing authorisation holder should send a justified request to the reference Member State for agreement.

The evaluation of responses may take up to 30 or 60 days depending on the complexity and amount of data requested to the marketing authorisation holder.

The request for supplementary information should be sent to the marketing authorisation holder together with a timetable stating the date by when the marketing authorisation holder should submit the requested data and where appropriate the extended evaluation period.

After receipt of the applicant's response, the reference Member State will prepare a draft assessment report according to the communicated timetable and will circulate it to the concerned Member States for comments as well as to the marketing authorisation holder for information. The concerned Member States should send their comments on the draft assessment report within the timeline as stated in the timetable.

### 2.3.3. Outcome of Type II variations assessment for national procedure

By the end of the communicated evaluation period, the reference Member State will finalise the assessment report including its decision on the application and send them to the concerned Member State.

Within 30 days following receipt of the assessment report and the decision, the concerned Member States shall recognise the decision and inform the reference Member State accordingly.

In case a concerned Member States identifies, within 30 days following receipt of the assessment report and the decision, a potential serious risk to public health, or, in the case of veterinary medicinal products, on grounds of a potential serious risk to human or animal health or to the environment, that prevents recognition of the decision, this Member State shall inform the reference Member State and give a detailed statement of the reasons for its position.

The reference Member State shall refer the application to the coordination groups for application of Article 33(3), (4) and (5) of Directive 2001/82/EC or Article 29(3), (4) and (5) of Directive 2001/83/EC to the matter of disagreement and will inform the marketing authorisation holder and the concerned Member States accordingly.

Where a grouped variations application is referred to the coordination group the whole grouped application will be suspended until a decision has been made, unless otherwise decided by the reference Member State. However, only the concerned variation(s) will be discussed by the coordination group and eventually by the Committee for Medicinal Products for Human use or the Committee for Veterinary Medicinal Products, not the whole group.

As with the initial marketing authorisation procedure, it should be noted that a referral to the coordination group by the applicant is not foreseen in the variations regulation.

The reference Member State will inform the concerned Member States and the marketing authorisation holder about the approval or rejection (including the grounds for the unfavourable outcome) of the variation(s). Where several Type II variations, or a group of Type II variation(s) with other minor variations have been submitted as one application, the reference Member State will inform the applicant and the concerned Member States which variation(s) have been accepted or rejected. The applicant may withdraw single variations from the grouped application during the procedure.

After a positive decision is communicated regarding variations with changes to the summary of product characteristics, labelling or package leaflet, the applicant should submit, within seven days, translations of the product information texts to all Member States concerned.

After approval of the variation(s), the competent authorities of the Member States concerned shall, where necessary, amend the marketing authorisation to reflect the variation(s) within two months or within 30 days when the variation leads to a six-month extension of the supplementary protection certificate as referred to in Article 13(1) and (2) of Council Regulation (EEC) No 1768/92, in accordance with Article 36 of Regulation (EC) No 1901/2006.

The accepted major variation(s) of Type II can be implemented 30 days after the marketing authorisation holder has been informed about the acceptance of the variation(s) by the reference Member State, provided that necessary documents to amend the marketing authorisation have been submitted to the Member State concerned.

Variations related to safety issues must be implemented within a time-frame agreed between the reference Member State and the holder.

#### 2.3.4. *Type II variations assessment for centralised procedure*

Upon receipt of a Type II application, the Agency will handle the application as follows:

If the application submitted to the Agency contains the elements listed in point 2.3.1, the Agency will acknowledge receipt of a valid application of a major variation of Type II. By the date of acknowledgement of the receipt of a valid application, the Agency will start the procedure. The marketing authorisation holder will be informed of the adopted timetable at the start of the procedure.

As a general rule, for major variations of Type II, a 60-day evaluation timetable will apply. This period may be reduced by the Agency having regard to the urgency of the matter, particularly for safety issues, or may be extended by the Agency to 90 days for variations concerning changes or additions to the therapeutic indication. For variations for veterinary medicinal products listed in Part 2 of Annex V of the variations regulation a 90-day timetable will apply.

Within the evaluation period, the Committee for Medicinal Products for Human Use or the Committee for Veterinary Medicinal Products may request supplementary information and adopt a timetable stating the date by when the marketing authorisation holder must submit the requested data and where appropriate the extended evaluation period.

The procedure will be suspended until the receipt of the supplementary information. As a general rule, a suspension of up to one month will apply. For suspension longer than one month the marketing authorisation holder should send a justified request to the Agency for agreement by the corresponding Committee.

For any follow-on request for supplementary information, an additional procedural suspension of up to one month will be applied in general; a maximum of two months may be applied when justified.

The Committee assessment of responses may take up to 30 or 60 days depending on the complexity and amount of data to be requested to the marketing authorisation holder.

The request for supplementary information or follow-on request should be sent to the marketing authorisation holder together with the timetable stating the date by when the marketing authorisation holder must submit the requested data and where appropriate the extended evaluation period.

An oral explanation to the Committee for Medicinal Products for Human Use or the Committee for Veterinary Medicinal Products may be held at the request of the Committee or the marketing authorisation holder, where appropriate.

#### 2.3.5. *Outcome of Type II variations assessment in centralised procedure*

Upon adoption of an opinion of the Committee for Medicinal Products for Human Use or the Committee for Veterinary Medicinal Products, the Agency will inform the marketing authorisation holder and the Commission within 15 days as to whether the opinion is favourable or unfavourable (including the grounds for the unfavourable outcome), as well as whether the Commission Decision granting the marketing authorisation requires any amendments. Where several Type II variations, or a group of Type II variation(s) with other minor variations have been submitted as one application, the Agency will issue an opinion reflecting the final outcome of the procedure. Such opinion will also list any variations which are not considered approvable. The applicant may withdraw single variations from the grouped application during the procedure.

The re-examination procedure set-out in Articles 9(2) and 34 (2) of Regulation (EC) No 726/2004 also applies to the opinions adopted for major variations of Type II applications.

Upon receipt of the final opinion, the Commission shall, where necessary, amend the marketing authorisation to reflect the variation(s) within two months or within 30 days when the variation leads to a six-month extension of the supplementary protection certificate.

Where a group of variations to the terms of one marketing authorisation submitted as part of one notification have been approved, the Commission will update the marketing authorisation with one single decision to cover all the approved variations.

The approved major variation(s) of Type II may only be implemented once the Commission has amended the decision granting the marketing authorisation and has notified the holder accordingly. Where any amendment of the decision granting the marketing authorisation are not required following the approval of a major variation of Type II, the approved variation may only be implemented once the marketing authorisation holder has been informed by the Commission accordingly.

Variations related to safety issues must be implemented within a time-frame agreed between the Commission and the holder.

## 2.4. Extensions

Annex I of the variations regulation sets-out a list of changes to be considered as extensions. As established in Article 19 of the variations regulation, such applications will be evaluated in accordance with the same procedure as for the granting of the initial marketing authorisation to which it relates. The extension will either be granted a new marketing authorisation or will be included in the initial marketing authorisation to which it relates.

### 2.4.1. Submission of Extensions applications

Extension applications must be submitted to all Member States concerned, or to the Agency,

Marketing authorisation holders may choose to group the submission of one or more extensions together with one or more other variations for the same product into one application, provided that this corresponds to one of the cases listed in Annex III of the variations regulation or when this has been agreed with the reference Member State or the Agency. However, no worksharing of extensions applications is foreseen in the variations regulation.

The application must be presented as follows, in accordance with the appropriate headings and numbering of the EU-CTD format or the Notice to applicants Volume 6B format (veterinary medicinal products when the EU-CTD format is not available):

- Cover letter.
- The completed EU application form (published in the Notice To Applicants).
- Supporting data relating to the proposed extension. Some guidance on the appropriate additional studies required for extension applications is available in Appendix IV to Chapter 1 of Volume 2A or 6A of the Notice to applicants.
- A full Module 1 (Part 1 for veterinary medicinal products) should be provided, with justifications for absence of data or documents included in the relevant section(s) of Module 1 or Part 1.
- Update or Addendum to quality summaries, non-clinical overviews and clinical overviews (or expert reports for veterinary medicinal products) as relevant. When non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2.
- In case that the extension affects the summary of product characteristics, labelling or package leaflet: the revised product information, presented in the appropriate format.

For extension applications in the national procedure, the reference Member State should additionally receive the list of dispatch dates indicating the procedure number, the dates on which the applications have been sent to each Member State concerned and confirmation that the relevant fees have been paid as required by national competent authorities.

For extensions in the centralise procedure, the relevant fee for the extension(s), as provided for in Council Regulation (EC) No 297/95, should be paid in accordance with the Agency's financial procedures.

### 2.4.2. Extension assessment for national procedure

Upon receipt of an extension application, it will be handled as an initial marketing authorisation application in accordance with Directive 2001/82/EC or Directive 2001/83/EC and Chapter 2 of the Notice to applicants — Volume 2A or 6A.

### 2.4.3. Extension assessment for centralised procedure

Upon receipt of an extension application, the Agency will handle the application as for an initial marketing authorisation application in accordance with Regulation (EC) No 726/2004.

## 2.5. Human influenza vaccines

Hereby guidance is provided on the application of Articles 12 and 18 of the variations regulation to the annual update of human influenza vaccines applications.

Because of the specificities inherent in the manufacturing of human influenza vaccines, a special 'fast track' variation procedure is applicable for the annual change in active substance for the purpose of the annual update of a human influenza vaccine in order to meet the EU recommendation for human influenza virus strain(s) vaccine composition for the coming season.

Any variations to human influenza vaccines other than the introduction of the annual update will follow the variation procedures foreseen in other sections of this Guideline. However, it is possible to handle such variations under a special urgent procedure, where necessary, in a pandemic situation as established in Article 21 of the variations regulation.

The 'fast track' procedure consists of two steps. The first part concerns the assessment of the administrative and quality data elements listed in Annex IV (summary of product characteristics, labelling and package leaflet, and the chemical, pharmaceutical and biological documentation). The second part concerns the assessment of the clinical data and data concerning the stability of the medicinal product.

Marketing authorisation holders are recommended to discuss the annual update submissions in advance with the reference Member State or the Agency.

### 2.5.1. Submission of variations for annual update of human influenza vaccines applications

Variations concerning changes to the active substance for the annual update of human influenza vaccines applications must be submitted to the reference Member State and to all concerned Member States, or to the Agency.

The application must be presented as follows, in accordance with the appropriate headings and numbering of the EU-CTD format:

- Cover letter.
- The completed EU application form (published in the Notice to applicants).
- Update or Addendum to quality summaries, non-clinical overviews and clinical overviews as relevant. When non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2. Chemical-pharmaceutical-biological supporting data relating to the proposed variation:

A revised chemical-pharmaceutical-biological expert report or an addendum to the current expert report. Furthermore, the following data are required:

Composition of the medicinal product

Clinical trial formula(e): actual formula (new season's strains)

Manufacturing formula: actual formula

Copy of approved specifications in a tabular format

Manufacturing process:

- seed lots: history:
  - passage level
  - characterisation of Haemagglutinin and Neuraminidase
  - analytical protocols (including test results on seed lots)
- monovalent bulks:
  - manufacturing process
  - strain specific changes
  - validation of critical manufacturing steps (new strain)
    1. inactivation
    2. splitting efficiency

Specific quality control testing: validation of SRD test for new strains.

Batch analysis results (monovalent bulks): results of the first three monovalent bulks from each working seed lot of new strains (including test for neuraminidase).

Copy of approved specifications and routine tests analytical methods in a tabular format.

Stability tests on the active substances: results from monovalent bulks where they are used for more than one year.

Stability tests on the finished product: results from the previous vaccine.

Commitment to report stability data of new vaccine if outside specifications.

Annual stability testing protocol. Clinical data supporting data relating to the proposed variation:

A revised clinical-pharmacological expert report or an addendum to the current expert report.

Results of clinical studies with the new vaccine are to be submitted as a short final report, including:

- raw data,
- characteristics of the trial population (demography, comorbidity, co-medication),
- standardised tables for immunogenicity and reactogenicity.

The type of serological test used should be stated clearly.

Applicants are encouraged to include the following PSURs in the clinical data package:

- PSUR covering the period 1 September-30 April of the previous season,
- PSUR covering the period 1 May-31 August of the last but one season.
- The revised product information, presented in the appropriate format.

For annual update of human influenza vaccines applications in national procedure, the reference Member State should additionally receive the list of dispatch dates indicating the procedure number, the dates on which the applications have been sent to each Member States concerned and confirmation that the relevant fees have been paid as required by national competent authorities.

For annual update of human influenza vaccines applications in centralised procedure, the relevant fee for the variation as provided for in Council Regulation (EC) No 297/95 shall be paid in accordance with the Agency's financial procedures.

#### 2.5.2. Variations assessment for national procedure

Upon receipt of an annual variation human influenza vaccines application, the reference Member State will handle the application as follows:

The reference Member State will acknowledge receipt of a valid application of an annual variation human influenza vaccine within seven days and inform the holder and the Member States concerned of the start of the procedure.

Within a maximum of 15 days from the start of the procedure, the reference Member State will send to the concerned Member States a preliminary assessment report on the administrative data and quality documentation. Concerned Member States should send their comments on the preliminary assessment within six days.

Within the evaluation period, the reference Member State may send the holder a request for supplementary information and inform the concerned Member States accordingly. The response document should be provided within a maximum of seven days. However, the procedure will not be suspended.

The reference Member State will prepare the final assessment report including its decision on the administrative data and quality part by day 30 from the start of the procedure.

The concerned Member States shall recognize the decision on the administrative and quality data within 12 days and will inform the reference Member State accordingly. The reference Member State will inform the marketing authorisation holder about the outcome.

Following the decision on the administrative and quality data, the marketing authorisation holder, where requested by the reference Member State has a maximum of 12 days to submit the clinical documentation and data concerning stability of the medicinal product to all Member States concerned.

The reference Member State will circulate the assessment report on the clinical documentation with its final decision to the concerned Member States within seven days from receipt of the clinical data.

The concerned Member States shall recognize that final decision and adopt a decision in accordance with the final decision within the following seven days.

#### 2.5.3. Variations assessment in centralised procedure

Upon receipt of an annual variation human influenza vaccines application, the Agency will handle the application as follows:

The Agency will acknowledge receipt of a valid application of an annual variation human influenza vaccine within seven days and inform the holder of the start of the procedure.

The Committee for Medicinal Products for Human Use has a maximum of 45 days from the start of the procedure to issue its initial opinion on the quality documentation submitted.

An adoption of a Committee for Medicinal Products for Human Use opinion or a request for supplementary information is foreseen at day 30. In case the Committee requests supplementary information, the marketing authorisation holder shall provide the answers within three days, and by day 45 the

Committee will adopt its opinion on the quality documentation. This opinion will be transmitted to the Commission that, where necessary, based on that opinion will adopt a decision on the variation to the terms of the marketing authorisation and inform the holder accordingly.

Following the opinion on the quality data, the marketing authorisation holder, where requested by the Agency, shall submit the clinical documentation and data concerning stability of the medicinal product to the Agency by day 57 at the latest. Upon receipt of this data, the Committee has a maximum of 10 days to adopt its final opinion which will be transmitted by the Agency to the Commission and to the marketing authorisation holder within a maximum of three days.

Where necessary and based on the final opinion from the Committee, the Commission will amend the decision granting the marketing authorisation and update the Community Register of Medicinal Products.

### 2.6. Urgent Safety Restrictions

Article 22 of the variations Regulation foresees that in the event of a risk to public health in the case of medicinal products for human use or in the event of a risk to human or animal health or to the environment in the case of veterinary medicinal products, the marketing authorisation holder may take provisional 'urgent safety restrictions'.

Urgent safety restrictions concern interim change(s) to the product information due to a pharmacovigilance, pre-clinical safety or quality signal which raise a serious concern which the marketing authorisation holder considers could represent a risk to human or animal health or to the environment and which must therefore be communicated immediately to prescribers and users; this new information has a bearing on the safe use of the medicinal product, concerning in particular one or more of the following items in the summary of product characteristics: therapeutic indications, posology, contra-indications, warnings, target species and withdrawal periods. These urgent changes will subsequently be introduced via a corresponding variation in the marketing authorisation.

The marketing authorisation holder must immediately notify all Member States concerned, or the Agency and the Commission, of the restrictions to be introduced.

If no objections have been raised by the relevant authority or the Commission within 24 hours following receipt of that information, the urgent safety restrictions are deemed as accepted. They must be implemented within a time frame agreed between the Commission or the reference Member State and the holder.

Such urgent safety restrictions may also be imposed by the Commission (for centrally authorised medicinal products) or by the national competent authorities (for nationally authorised medicinal products) in the event of a risk to public health in the case of medicinal products for human use or in the event of a risk to human or animal health in the case of veterinary medicinal products.

The corresponding variation application reflecting the urgent safety restrictions (whether requested by the holder or imposed by the Commission or the national competent authorities) must be submitted as soon as possible within 15 days after the initiation of the urgent safety restrictions.

### 3. PROCEDURAL GUIDANCE ON WORKSHARING

Article 20 of the variations Regulation sets-out the possibility for a marketing authorisation holder to submit in one application the same Type IB, the same Type II variation, or the same group of variations corresponding to one of the cases listed in Annex III of the Regulation or agreed with the reference Member State or the Agency which does not contain any extension affecting more than one marketing authorisation from the same holder.

In order to avoid duplication of work in the evaluation of such variations, a worksharing procedure has been established under which one authority (the 'reference authority'), chosen amongst the competent authorities of the Member States and the Agency, will examine the variation on behalf of the other concerned authorities.

Where at least one of the concerned marketing authorisations has been authorised via the centralised procedure, the Agency will be the reference authority (section 3.4). In all other cases, a national competent authority chosen by the coordination group, taking into account the recommendation of the holder, will act as the reference authority (section 3.2).

In order to facilitate the planning of the procedure, marketing authorisation holders are encouraged to inform the Agency or the coordination group and the proposed reference authority at least three months in advance of the submission of a variation or group of variations to be subject to a worksharing procedure.

In order to benefit from a worksharing procedure, it is expected that the same change(s) will apply to the different medicinal products concerned, with either no or limited need for assessment of a potential product-specific impact. Therefore, where the 'same' change(s) to different marketing authorisations require the submission of individual supportive data sets for each medicinal product concerned and separate product-specific assessment, such changes will not benefit from worksharing.

#### 3.1. Submission of variation(s) application under worksharing

A variation or group of variations presented for worksharing should be submitted as set-out in sections 2.2-2.3 above and

should be provided as one integrated submission package covering all variations for all medicinal products. This will include a common cover letter and application form, together with separate supportive documentation for each medicinal product concerned and revised product information (if applicable) for each medicinal product concerned. This will allow the Agency and the national competent authorities to update the dossier of each marketing authorisation included in the worksharing procedure with the relevant amended or new information.

The worksharing application must be submitted to all relevant authorities, i.e. for centralised procedure, the Agency and all Member States where the products concerned are authorised.

#### 3.2. Worksharing assessment for national procedure

When the marketing authorisation holder informs the coordination group of an upcoming worksharing procedure, the coordination group will at the following meeting decide on the reference authority, taking into account the proposal of the holder and, if applicable pursuant to the third subparagraph of Article 20(3) of the variations regulation, another relevant authority to assist the reference authority. The marketing authorisation holder will be informed by the coordination group of the decision of which national competent authority will act as reference authority.

Upon receipt of a worksharing application, the reference authority will handle the application as follows:

The reference authority will acknowledge receipt of a valid application for worksharing. Immediately after acknowledging receipt of a valid application, the reference authority will start the procedure. The marketing authorisation holder and the Member States concerned will be informed of the timetable at the start of the procedure.

In general, worksharing procedures will follow a 60-day evaluation timetable or a 90-day evaluation timetable for variations listed in Part 2 of Annex V of the variations regulation. This period may however be reduced by the reference authority having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 days evaluation timetable where variations listed in Part 1 of Annex V of the variations regulation are part of the worksharing procedure.

The reference authority prepares the a draft assessment report according to the communicated timetable and circulates it to the concerned Member States for comments as well as the marketing authorisation holder for information. Concerned Member States should send their comments to the draft assessment report within the timeline stated in the timetable.

Within the evaluation period, the reference authority may send to the marketing authorisation holder a request for supplementary information.

The procedure will be suspended until the receipt of the supplementary information. As a general rule, a suspension of up to one month will apply. For longer suspension the marketing authorisation holder should send a justified request to the reference authority for agreement.

The assessment of responses may take up to 30 or 60 days depending on the complexity and amount of data requested to the marketing authorisation holder.

The request for supplementary information should be sent to the marketing authorisation holder together with a timetable stating the date by when the marketing authorisation holder must submit the requested data and where appropriate the extended evaluation period.

After receipt of the applicant's response, the reference authority will finalise the draft assessment report on the application and circulate it to the concerned Member States and to the marketing authorisation holder for information within the timeline as stated in the timetable. Concerned Member States should send their comments on the final draft assessment report within the timeline as stated in the timetable.

### 3.3. Outcome of the assessment for national procedure

Upon finalisation of the review of the variations subject to the worksharing procedure, the reference authority will issue its opinion reflecting the final outcome.

In case of a favourable decision in the worksharing application the reference authority will inform the applicant and the concerned Member States about the approval of the worksharing. Such opinion will also list any variations (e.g. as part of a group, or for a specific medicinal product) which are not considered approvable.

In case of an unfavourable decision, the reference authority will inform the applicant as well as the concerned Member States about refusal of the worksharing application (including the grounds for the unfavourable outcome).

Within 30 days following receipt of the opinion, the concerned Member States shall approve the opinion, and inform the reference Member State and amend the concerned marketing authorisations accordingly.

In case one of the concerned Member States identifies, within 30 days following receipt of the opinion, a potential serious risk to public health, or, in the case of veterinary medicinal products, a potential serious risk to human or animal health or to the environment, this Member State shall inform the reference authority accordingly and the reference authority shall refer the application to the coordination group for application of Article 33(3), (4) and (5) of Directive 2001/82/EC or Article 29(3), (4) and (5) of Directive 2001/83/EC to the matter of disagreement.

A referral to coordination group by the applicant is not foreseen in the variations regulation.

After a positive opinion is communicated regarding variations with changes to the summary of product characteristics, labelling or package leaflet, the applicant should submit, within seven days, translations of the product information texts to all Member States concerned.

Minor variation(s) of Type IB approved via a worksharing procedure, may be implemented upon receipt of the favourable opinion of the reference authority.

Major variation(s) of Type II (including those which contain grouped minor variation(s) of Type IB) approved via a worksharing procedure may be implemented 30 days after receipt of the favourable opinion from the reference authority, unless the application have been referred to the coordination group for application of Article 33(3), (4) and (5) of Directive 2001/82/EC or Article 29(3), (4) and (5) of Directive 2001/83/EC to the matter of disagreement.

Variations related to safety issues must be implemented within a time-frame agreed between the marketing authorisation holder and the reference authority.

### 3.4. Worksharing assessment for centralised procedure

Upon receipt of a worksharing application, the Agency will handle the application as follows:

The Agency will acknowledge receipt of a valid worksharing application. Immediately after acknowledge receipt of a valid application, the Agency shall start the procedure. The marketing authorisation holder will be informed of the adopted timetable at the start of the procedure.

The Agency will appoint a rapporteur (and in some cases also a co-rapporteur) to lead the assessment procedure.

In general, worksharing procedures will follow a 60-day evaluation timetable or a 90-day evaluation timetable for variations listed in Part 2 of Annex V of the variations regulation. This period may however be reduced by the reference authority having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 days evaluation timetable where variations listed in Part 1 of Annex V of the variations regulation are part of the worksharing procedure.

Within the evaluation period, the Committee for Medicinal Products for Human Use or the Committee for Veterinary Medicinal Products may request supplementary information and adopt a timetable stating the date by when the marketing authorisation holder must submit the requested data and the extended evaluation period, if needed.

The procedure will be suspended until the receipt of the supplementary information. As a general rule, a suspension of up to one month will apply. For suspension longer than one month the marketing authorisation holder should send a justified request to the Agency for agreement by the Committee for Medicinal Products for Human or the Committee for Veterinary Medicinal Products.

For any follow-on request for supplementary information, an additional clock-stop of up to one month will be applied in general; a maximum of two months may be applied when justified.

The Committee assessment of responses may take up to 30 or 60 days depending on the complexity and amount of data provided by the marketing authorisation holder.

The request for supplementary information or follow-on request should be sent to the marketing authorisation holder together with a timetable stating the date by when the marketing authorisation holder must submit the requested data and where appropriate the extended evaluation period.

An oral explanation to the Committee for Medicinal Products for Human Use or the Committee for Veterinary Medicinal Products can be held at the request of the relevant Committee or the marketing authorisation holder, where appropriate.

### 3.5. Outcome of the assessment in centralised procedure

Upon finalisation of the review of the variations subject to the worksharing procedure, the Agency will issue an opinion reflecting the final outcome of the procedure. Such opinion will also list any variations (e.g. as part of a group, or for a specific medicinal product) which are not considered approvable.

Upon adoption of the opinion of the Committee on the work-sharing procedure, the Agency will inform the marketing authorisation holder, the Commission and Member States concerned (if applicable) as to whether the opinion is favourable or

unfavourable (including the grounds for the unfavourable outcome), as well as whether the Decision granting the EU marketing authorisation requires any amendments.

The re-examination procedure set-out in Articles 9(2) and 34(2) of Regulation (EC) No 726/2004 also applies to opinions adopted for worksharing procedures.

Upon receipt of the final opinion, the Commission shall, where necessary, amend the EU authorisations within 30 days and the Member States concerned (if applicable) shall approve the final opinion, inform the Agency accordingly and where necessary, amend the national marketing authorisations within 30 days, unless a referral procedure in accordance with Article 35 of Directive 2001/82/EC or Article 31 of Directive 2001/83/EC is initiated within 30 days following receipt of the final opinion.

For a worksharing application to the terms of several marketing authorisations owned by the same holder, the Commission decision will apply only for centrally authorised products. If the variation concerns more than one centrally authorised product, the update to marketing authorisations will be one decision per centrally authorised product.

Minor variations of Type IB approved via the worksharing procedure, may be implemented upon receipt of the favourable opinion.

Major variation(s) of Type II (including those which contain grouped minor variation(s) of Type IB) approved via a work-sharing procedure may be implemented 30 days after receipt of the favourable opinion from the Agency, unless a referral procedure in accordance with Article 35 of Directive 2001/82/EC or Article 31 of Directive 2001/83/EC is initiated within 30 days following receipt of the final opinion

Variations related to safety issues must be implemented within a time-frame agreed between the marketing authorisation holder and the Commission.

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