1. Introduction

In accordance with Directives 65/65/EEC and 81/851/EEC, a marketing authorisation for a medicinal product is granted for a period of 5 years, renewable upon application three months before expiry. Throughout the life of a medicinal product, the holder of the authorisation is responsible for the product which circulates in the marketplace and is also required to take into account technical and scientific progress, and to make any amendments that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. Such amendments must be approved by the competent authority.

Marketing authorisation holders may, in addition, wish to alter/improve the medicinal product or to introduce an additional safeguard during the period of five years. Such changes or “variations” may involve administrative and/or more substantial changes, and procedures for the approval of such changes, have been in operation for some years in most Member States.

With the implementation of the new system of marketing authorisation, and given the need to maintain achieved harmonisation, it became necessary to codify variations and to set out common procedures which, on the one hand facilitate the task of both industry and authorities and on the other hand, guarantee that changes to the medicinal product do not give rise to public health concerns. Therefore two Regulations have been introduced, Regulation (EEC) No. 541/95 and 542/95.

For the operation of the procedures set out by these regulations, the following documents have been prepared:

- a procedural guidance for the Member States (reference or concerned) and the applicant for variations in the mutual recognition procedure;
- a procedural guidance for the applicant for variations in the centralised procedure;
- a common application form which may be used for variations Type I or II, in both the centralised and mutual recognition procedures;
- a guideline on the documentation to be submitted for Type I variations.

2. Changes to a marketing authorisation

2.1 Variations

To take account of the different needs for changes to a marketing authorisation, the Regulations have classified variations into two types:

"Type I": These variations are listed in Annex 1 of the Regulations and concern an amendment to the contents of the documents (1) such as they existed at the moment the

(1) Article 6 (1) and (2) of Council Regulation (EEC) No 2309/93; Article 4 of Directive 65/65/EEC.
decision on the marketing authorisation. Conditions which must be fulfilled are set out in the same annex.

"Type II": any change to the documentation proposed by the marketing authorisation holder, which is not a type I variation and does not require a new application procedure is considered as a type II variation.

"Urgent Safety Restriction": an interim change to product information by the marketing authorisation holder restricting the indication(s), and/or dosage, and/or target species of the medicinal product; or adding a contra-indication, and/or warning due to new information having a bearing on the safe use of the product.

The marketing authorisation holder (MAH) is responsible for the product being marketed and for monitoring the continued safety in use of that product. In the event that a pharmacovigilance, pre-clinical safety or quality signal raises a concern which the MAH considers must be communicated immediately to prescribers and users by a restriction of the indication(s)/dosage and/or addition of a contra-indication/warning, the MAH may take provisional urgent safety restrictions in the event there is a risk to public or animal health. The holder shall forthwith inform the competent authorities and if any objections are not raised within 24 hours, the urgent safety restrictions may be introduced and the corresponding application for this variation shall be submitted without delay.

2.1 Changes to the labelling or package leaflet

Changes to an aspect of the labelling or the package leaflet covered by Council Directive 92/27/EEC on the labelling of medicinal products for human use and on package leaflet and not connected with the summary of product characteristics are examined in accordance with Article 10, para. 3 of that Directive i.e. the proposed changes are submitted to the authority competent for marketing authorisation. If the competent authority has not opposed a proposed change within 90 days following the introduction of the request, the applicant may put the change into effect.

Changes to an aspect of the labelling or package leaflets of medicinal products for human use connected with the summary of product characteristics follow the procedure foreseen for variations - Type I or II as appropriate.

2.3 Change in the content of the manufacturing authorisation

Manufacture of medicinal products is subject to the holding of an authorisation. This manufacturing authorisation shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation and for imports coming from third countries into a Member State.

If the holder of a manufacturing authorisation requests a change in any of the particulars, the time taken for the procedure relating to this request shall not exceed 30 days. In exceptional cases this period of time may be extended to 90 days.

Member States may require from the applicant further information concerning the particulars supplied and concerning the qualified person; where the competent authority concerned exercises this right, application of the time limits referred above shall be suspended until the additional data required have been supplied.
After the above change has been approved, a variation application (Type I, number 1) is only required when the information relating to the authorisation to manufacture the medicinal product concerned is changed.

**Procedural guidance for mutual recognition variations**

The following operational scheme is intended as a guide when processing variations.

The procedure for processing Type I and Type II variations is outlined with respect to:
- action to be taken by the Reference Member State
- action to be taken by the Concerned Member States
- action to be taken by the Applicant

The communication pages of the Application Form (page 1 and the appendix) may be used to notify decisions and communicate information to applicants and between Member States. The timetable for each stage of the process will be notified by the RMS using the Appendix of the Application Form.

### 3. Mutual recognition variations - Type I

#### 3.1 Action by the Reference Member State (RMS) - Type I variation

<table>
<thead>
<tr>
<th>Day 0</th>
<th>• Notify applicant and CMS of start date, or that application is invalid.</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
<td>• Assess variation application</td>
</tr>
<tr>
<td>By Day 20</td>
<td>• Receive objections from CMS (if any)</td>
</tr>
<tr>
<td>↓</td>
<td>• Review objections</td>
</tr>
<tr>
<td>By Day 29</td>
<td>• Make a decision and take action</td>
</tr>
<tr>
<td>↓</td>
<td>• Notify CMS of the decision and if non-favourable the reasons for objection.</td>
</tr>
<tr>
<td>By Day 30</td>
<td>• Favourable - applicant may be notified</td>
</tr>
<tr>
<td>↓</td>
<td>• Non-favourable - notify applicant of the grounds for non-acceptance. Applicant has 30 days to respond.</td>
</tr>
<tr>
<td>Day 60</td>
<td>• No amendment received.</td>
</tr>
<tr>
<td></td>
<td>• Formal refusal to applicant on behalf of all CMS.</td>
</tr>
<tr>
<td></td>
<td>• Notify CMS</td>
</tr>
<tr>
<td>---</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>• Amendment received by RMS and CMS</td>
</tr>
<tr>
<td>---&gt;</td>
<td>New Day 0 • Notify applicant and CMS of new start date. If CMS advises amendment not received, RMS to stop clock.</td>
</tr>
</tbody>
</table>
• Assess variation amendment.
By Day 20 • Receive objections from CMS (if any).
↓ • Review objections and discuss with member states, as necessary.
By Day 29 • Make a decision and take action
↓ • Notify CMS of decision
By Day 30 • Favourable - applicant will be notified
↓ • Non favourable - formal refusal to applicant on behalf of all
CMS Indicate if there is a divergent position
• Notify CMS
By Day 40 • Applicant may request arbitration

### Key duties for RMS - Type I

- Notify applicant and CMS of procedure start date.
- By day 30, variation is approved or send notification of the grounds for non-acceptance to applicant. Notify CMS.
- If applicant amends application, notify applicant and CMS of new procedure start date. Stop clock if any CMS advises that amendment is not received.
- By new day 30 (with up to 30 days clock off), approve or refuse variation. Notify CMS.

### 3.2 Action by the concerned Member States (CMS) - Type I variation

- Receive variation application with fee.
- Validation. (Check for correct fee and language requirements).
- Confirm receipt of valid application to Reference Member State (RMS). Send copy to applicant.
- In exceptions, where there is a problem, request applicant to rectify problem and immediately notify RMS of reasons for delay. Send copy to applicant.

Day 0 • Notified of procedure start date by RMS.
↓ • Assess variation application
By Day 20 • Notify RMS of objections (if any)
↓ •

--- By Day 30 • Notified of decision and if non-favourable the grounds for non-acceptance

Day 60 • Notified of refusal if no amendment received.

--- New Day 0 • Amendment received by RMS and CMS.

---> New Day 0 • Notified of new start date by RMS.

• Immediately advise RMS if amendment not received. RMS will stop clock.

By Day 20 • Consider the variation amendment and notify RMS by day 20 if any objections.
↓
By Day 30 • Notified of decision
• Favourable – applicant will be notified by RMS. CMS may notify applicant.

↓

• Non-favourable – formal refusal by RMS. CMS may notify applicant.

By Day 40

• Applicant may request arbitration

• Comments to RMS as requested

**Key duties for CMS – Type I**

- Notify RMS immediately on receipt of valid application or reasons for delay. Copy applicant.
- By day 20, notify RMS of grounds for non-acceptance (exceptional).
- Advise RMS immediately if amendment has not been received from applicant following receipt of new start date. RMS will stop clock.
- By new day 20, notify RMS of any further objections (exceptional).

### 3.3 Action by the applicant – Type I variation

**a) General approach**

The EC application form “Application for Variation to a Marketing Authorization” should always be used. The application form should be completed taking account of the guidance notes for the completion of the application form for variation to a marketing authorisation – see Section 4.2 of this chapter.

The correct number of copies of the completed application form and the supporting data, in an appropriate language (see chapter VII), and the correct fee should be despatched *simultaneously* to the RMS and each of the CMS. It is important to ensure as far as possible that the RMS and each of the CMS receive the application preferably on the same day. A covering letter should be included with each application form, and this should indicate: the product name in each CMS (including the RMS) and the dates on which the variation application has been sent to the RMS and CMS. For all mutual recognition applications the applicant should send a copy of the application form to the EMEA.

Where revised SPCs or label or label/insert are included as part of an application, each of the revisions to these documents should be highlighted.

It is important to be aware that although a number of CMS may elect to notify the applicant of the following, only the RMS is actually required to do this:

- clock start dates
- grounds for non-acceptance of type I variations
- refusal of type I variations
- approval of type I variations

The RMS will forward the notifications only to the address of the company stated on the application form submitted to the RMS. It is up to the applicant to copy this advice to each of their relevant offices in the other CMS, as appropriate.
If a variation application is to be withdrawn, this may only be done in advance of the initiation or trigger of arbitration proceedings (that is the company letter requesting arbitration) and the application must be withdrawn simultaneously from all Member States.

b) Specific approach

1. Ensure that the conditions specified for the type I variation are met and that all of the data requirements specified in the EC guideline “Dossier requirements for type I variations” are fulfilled.

2. Each CMS will notify the RMS of receipt of a variation application and will indicate whether or not the application is considered to be valid. These notifications will be copied to the applicant. If a CMS has not copied such a notification to the applicant 7 days from the date on which they should have received the application, the applicant should investigate the reasons for this and contact the relevant CMS if appropriate.

3. The RMS will advise the applicant of the clock start date. If the applicant has not received advice of grounds for non-acceptance of the variation by either the RMS or any of the CMS, 30 days after the clock start, the variation may be implemented.

4. If any of the Member States cannot agree to the application then the RMS will advise the applicant of the grounds for non-acceptance within 30 clock days.

5. If no action is taken by the applicant within 30 days of receipt of the grounds for non-acceptance the application is refused.

6. To pursue the variation, by addressing the grounds for non-acceptance an amendment to the variation application and supporting data (to include additional data if relevant or revised documents such as the SPC) can be made by the applicant. This amendment must be submitted to the RMS and each of the CMS simultaneously and must arrive at both RMS and each of the CMS within 30 days of receipt of the grounds for non-acceptance. The correct number of copies of the amendment in an appropriate language should be submitted.

7. The RMS will advise the applicant of the new clock start date for the amended application.

8. If the amended application is acceptable then the applicant will be informed by the RMS that the amended application has been approved.

9. If the amended variation is unacceptable the applicant will be advised within 30 days from the new clock start, normally by the RMS, of the refusal of the application. The RMS will indicate whether or not the Member States decisions were divergent.

10. If the rejection is based on a divergent decision of the Member States, and the applicant wishes to refer the matter for arbitration this must be done by advising the RMS, all CMS and the EMEA of this within 10 days of receipt of the refusal.
4. Mutual recognition variations - Type II

4.1 Action by the Reference Member State - Type II variation

- Receive variation application with fee.
- Validation. (Check for correct fee, application form, justification for consequential variations, supporting data, amended documents).
- Advise Concerned Member States (CMS) of European Procedure Number and co-ordinate procedure start date.
- Receive notification of receipt from CMS. RMS to check with CMS if no response.

Day 0
- Notify applicant and CMS of start date.
- Indicate to CMS a date (up to day 40) by when a preliminary variation assessment report (VAR) will be available.

↓
By Day 40
- Assess variation application

↓
By Day 55
- Receive any contribution from CMS for inclusion in VAR or supplementary information request
By Day 59
- Send one request for supplementary information as appropriate (60 days clock off). Negotiate additional time with applicant as necessary.

↓
- Notify CMS of request to applicant

↓
- Consider response from applicant and discuss any issues with CMS who raised objections.

By Day 60
- Circulate finalised VAR to CMS with draft decision.
By Day 85
- Receive notification from CMS of acceptance/non-acceptance of VAR decision.

Days 85 to 90
- In cases of a likely divergent position or refusal, RMS to liaise with applicant, so applicant may withdraw in all member states.

By Day 90
- Agreement between Member States - formal approval or refusal to applicant
- Notify CMS of decision, and for approvals the date of the effect of the decision.
- Disagreement between member states - binding arbitration. Notify CMS and CPMP/CVMP and applicant.
- Non-favourable - notify applicant of the reasons for objection.
- Adoption of decision and date of its effect.
- Formal approval or refusal of variation notified to applicant.
Chapter 5    Variations

Key duties for RMS - Type II

- Notify applicant and CMS of procedure start date.
- Indicate to CMS a date by when a preliminary information to the application, if necessary.
- By day 59, send a request for supplementary information to the applicant, if necessary.
- By day 60 (extended if further information requested), send finalised assessment report and draft decision to CMS.
- Between days 85 and 90, liaise with applicant if a divergent position or refusal is likely, so applicant has opportunity to withdraw variation in all member states.
- If there is unanimous agreement between member states, notify CMS of final decision and, for approvals, copy CMS with the letter to applicant which notifies the date of the effect of the decision.
- In the case of a divergent position, participate in arbitration procedure.
- Approve or refuse variation.

4.2 Action by the concerned Member States (CMS) - Type II Variation

- Receive variation application with fee.
- Validation. (Check for correct fee and language requirements).
- Confirm receipt of valid application to Reference Member State (RMS). Send copy to applicant.
- In exceptions, where there is a problem, request applicant to rectify problem and immediately notify RMS of reasons for delay. Send copy to applicant.

Day 0
- Notified of procedure start date by RMS and date by when preliminary variation assessment report (VAR) will be available.
- Decide the extent (if any) of assessment to undertake before receipt of VAR.

By Day 40
- Receive preliminary VAR from RMS.

By Day 55
- Send any contributions to RMS for inclusion in VAR or supplementary information.

By Day 59
- Receive copy of request from RMS for supplementary information.
- Receive additional data from applicant
- Discussion with RMS, as requested

By Day 60
- Receive finalised VAR from RMS

By Day 85
- Notify RMS of acceptance/non-acceptance of VAR decision

By Day 90
- Agreement between MS - formal approval or refusal issued to applicant.
• Involvement in binding arbitration if agreement is not reached.
• Adoption of decision and date of its effect.
• Formal approval or refusal of variation notified to applicant.

**Key duties for CMS – Type II**

- Notify RMS immediately on receipt of valid application, or reasons for delay. Copy to applicant.
- By day 55, advise RMS of any contributions for inclusion in the VAR or the request for supplementary information.
- By day 85, advise RMS whether or not the conclusion of the assessment report is acceptable.
- Participate in arbitration procedure.
- Approve or refuse variation.

### 4.3 Action by the applicant - Type II variation

**a) General approach**

The EC application form “Application for Variation to a Marketing Authorization” should always be used. The application form should be completed taking account of the guidance notes for the completion of the application form for variation to a marketing authorisation – see Section 4.2 of this chapter. For Type II variations involving a complex change the applicant should liaise with the RMS before submission.

The correct number of copies of the completed application form and the supporting data, in an appropriate language (see Chapter VII), and the correct fee should be despatched **simultaneously** to the RMS and each of the CMS. It is important to ensure as far as possible that the RMS and each of the CMS receive the application preferably on the same day. A covering letter should be included with each application form, and this should indicate: the product name in each CMS (including the RMS), the marketing authorisation holder’s name and address in each CMS (including the RMS) and the dates on which the variation application has been sent to the RMS and CMS. For all mutual recognition applications the applicant should send a copy of the application form to the EMEA.

Where revised SPCs or label or leaflet/insert are included as part of an application, each of the revisions to these documents should be highlighted.

It is important to be aware that although a number of CMS may elect to notify the applicant of the following, only the RMS is actually required to do this:

- clock start dates
- requests for supplementary information

The RMS will forward these notifications only to the address of the company stated on the application form forwarded to the RMS. It is essential that this office copies this advice to each of their relevant offices in the other CMS.

If a variation application is to be withdrawn, this may only be done in advance of the initiation or trigger of arbitration proceedings (that is before Day 90) and the application must be withdrawn simultaneously from **all** member states.
b) Specific approach

1. Ensure that the criteria for submitting a new MA application do not apply.
2. Ensure that the supporting data are complete.
3. Reference to the EC “Guideline on the Variation Assessment Report” may be useful.
4. Each CMS will notify the RMS of receipt of a variation application and will indicate whether or not the application is considered to be valid. These notifications will be copied to the applicants. If a CMS has not copied such a notification to the applicant 7 days from the date on which they should have received the application, then the applicant should investigate the reasons for this and contact the relevant CMS if appropriate.
5. The RMS will advise the applicant of the clock start date.
6. Within 60 days of the clock start date, the RMS may require the applicant to submit supplementary information.
7. Normally the supplementary information should be sent simultaneously to the RMS and each of the CMS within 60 days of the request. If it is impossible to provide the necessary information within this period, the applicant should advise the RMS of this and extended period of time in which to provide the data may be requested. This additional period of time should not normally exceed 60 days and the date for provision of the data must be agreed with the RMS. The clock will remain stopped from the time that the request for supplementary information is made until the RMS and each of the CMS have received the supplementary information.
8. Between days 85 and 90, the RMS will liaise with the applicant if a divergent position between member states or refusal is likely. The applicant has the opportunity to withdraw the variation at this stage from all Member States.
9. On or before 90 days of the clock have elapsed the applicant will be advised that the application is either approved or refused or that it has been referred for arbitration.
10. The RMS will communicate to the applicant the outcome of discussions with member states concerning the date of the effect of the decision.
11. The applicant will receive formal approval or refusal of the variation from the RMS and all CMS.

5. Procedural guidance for centralised variations

The procedures for approval of “variations” to the terms of a marketing authorization which have been granted in accordance with Council Regulation (EEC) No 2309/93 are set out in Commission Regulation (EC) No 542/95 of 10 March 1995.

In accordance with the abovementioned Regulation a variation to the terms of a Marketing Authorization means an amendment to the contents of the documents and particulars referred to in Article 6(1) and (2) of Council Regulation (EEC) No 2309/93, such as they existed at the moment of the decision on the marketing authorization or after approval of any previous variation.
In this Regulation, variations are defined to fall into two categories: Type I (minor variations) and Type II (major variations).

It should be noted, however, that under the same Regulation, certain categories of medicinal products, i.e. biotech medicinal products falling under List A of Council Regulation (EEC) No 2309/93, immunological medicinal products consisting of vaccines, toxins or serums and allergens and medicinal products derived from human blood or human plasma, for certain Type I categories the Type II approval procedure is followed, although a Type I fee will apply.

5.1 Preliminary steps

The applicants are advised to contact the EMEA Secretariat at least one month before the intended date for submission of the application for a variation. A justification for the type of variation should be provided. Applicants should consult with the EMEA for the best strategy when they intend to submit more than one variation application.

A project manager will be appointed in all cases. For certain Type I and for all Type II variations, a Rapporteur and, if appropriate, a Co-Rapporteur will be nominated. In principle, they would remain the same as those appointed for the evaluation of the application of the marketing authorisation to which the variation is relating.

The applicant should make use of the European Variation Application Form available from the EMEA.

The applicant shall submit a separate application for each variation. Nevertheless, where a variation entails more than one further change, a single application may cover all such consequential variations, where the applicant describes the relation between the main variation and its consequential variations.

The application for the variation should be submitted simultaneously to the EMEA and to the Rapporteur, wherever one has been appointed. In addition, for type II variations, the documentation should also be sent to those CPMP members who would wish to receive it.

5.2 Procedure for obtaining a Type I variation

The applicant should ensure that the specific conditions for the Type I variation have to be met, and that the application form (available at the EMEA) should be accompanied by:

- supporting data relating to the variation applied for as specified in the Guideline “Dossier requirements for Type I variations”;
- all documents amended as a consequence of the application; with a reference to those to be substituted from the original dossier;
- if appropriate, amendments to be introduced in the Commission Decision granting the marketing authorisation, translated in all official languages of the EU;
- payment of the fee.

The application would be validated by the EMEA Secretariat within 5 working days. Once validated the clock starts and the applicant, the Rapporteur and other CPMP members will be informed accordingly.

In the absence of any reaction from the Agency, within 30 days after the start of the clock, the variation is deemed to have been accepted and can be implemented by the Company.
Within 30 days after the start of the clock, the EMEA shall inform the Commission of the variation to be made to the terms of the marketing authorisation.

If the EMEA Secretariat, in consultation with the CPMP, is of the opinion that the application can not be accepted it informs the company within 30 days, allowing the company to amend the application within 30 days.

Once the application is amended, it will be evaluated in 30 days.

If no action is taken by the applicant within 30 days of receipt of the grounds for non acceptance, the application shall be deemed to have been rejected.

The Commission, where necessary, amends the Community Marketing authorisation retroactively.

For certain products (i.e. biotechnological medicinal products falling under list A of Council Regulation 2309/93, immunological medicinal products consisting of vaccines, toxins or serums and allergens, and medicinal products derived from human blood or human plasma), the opinion on type I variations Nos. 11, 12, 13, 14, 15, 16, 17, 24, 25 and 30 of the Annex I to Commission Regulation (EC) No 542/95, should be processed through the type II procedure, whilst the fee remains a Type I variation fee.

5.3 Procedure for obtaining a Type II variation

For organisational purposes, and given that the validation should be done within 5 working days, applicants are invited to submit their application for type II variations during the week preceding CPMP meetings.

The application form should be accompanied by:

- supporting data relating to the variation applied for;
- all documents amended as a consequence of the application; with a reference to those to be substituted from the original dossier;
- an Addendum to or an update to the existing expert report(s) to take into account the variation applied for;
- payment of the fee.

The application is validated by the EMEA Secretariat within five working days following submission. Once validated the applicant, the Rapporteur and other CPMP members are informed, the timetable is adopted and the clock starts accordingly.

The opinion is issued by the CPMP within the following 60 days. At around day 60 from the start of the procedure, at a plenary CPMP meeting, the CPMP adopts its opinion. In accordance with Article 7.2 of Commission Regulation (EC) No 542/95, this period may be extended by a further 60 days (or more) when additional information is requested by the CPMP.

a) Where the CPMP delivers a favourable opinion, the EMEA shall inform the Holder of the Marketing Authorisation and the Commission immediately, and shall send the Commission the amendments to be made to the terms of the Marketing Authorisation accompanied by the following documents as appropriate:

• manufacturing and/or importing conditions and conditions of the marketing authorisation;
• a draft Labelling and Package leaflet presented in accordance with Council Directive 92/27/EEC;
• a classification for the supply of the medicinal product;
• the CPMP assessment report (variation assessment report).

Where appropriate, divergent positions of Committee Members with their grounds.

b) Where the CPMP delivers an unfavourable opinion, the appeal procedure shall apply in accordance with Article 9 of Council Regulation (EEC) No 2309/93 (i.e. the applicant may appeal within 15 days as from the receipt of the opinion).

In case of a negative opinion, the following documents must be attached to the CPMP opinion:
• the appended Committee's variation assessment report stating the reasons for its negative conclusions.
• where appropriate, and upon Members' request, divergent positions of Committee Members with their grounds.

The Commission Decision varying the terms of the Marketing Authorisation is adopted in accordance with the procedure laid down in Article 9 of Council Regulation (EEC) No 2309/93 and Commission Regulation (EC) No 1662/95.

The Community Register of Medicinal Products will be updated as necessary.

5.4 Changes imposed by the need to adopt urgent safety restrictions

In the event of risk to public health, the holder of a Marketing Authorisation may introduce provisional urgent safety restrictions which may then eventually be introduced via a corresponding variation in the Marketing Authorisation.

In such a case, the Marketing Authorisation Holder shall immediately notify the EMEA, the Rapporteur, the Co-Rapporteur and Member States of the provisional restrictions introduced.

If the EMEA has not raised any objections within 24 hours, the Marketing Authorisation Holder shall implement the urgent safety restrictions and submit without delay to the EMEA and Rapporteur an application for the variation of the terms of the Marketing Authorisation. The corresponding variation application should be handled in accordance with the procedure laid down in Commission Regulation (EC) No. 542/95 for Type II variations as described above.
6. Application form for a variation to a Marketing Authorization

COMMUNITY AUTHORIZATION ☐ NATIONAL AUTHORIZATION ☐

FOR NATIONAL MA s: WAS MUTUAL RECOGNITION PROCEDURE USED? If YES, state number _______
Reference Member State __________ Concerned Member States __________

Type I ☐ Type II ☐ Urgent safety restriction (Type II) ☐

(Please tick the appropriate category of the variation and where appropriate state abbreviation for MSs)

Product name: ______________________________
Active substance(s)/quantitative:
Pharmaceutical form: _______________________
MA number: ________________________________
Applicants reference: ________________________

Name and address of MA holder:

Contact: ____________________________________
Telephone number: _________________________
Fax number: _______________________________

(For Official Use Only) NOTIFICATION TO APPLICANT

Please quote the MA number and the following reference in any future correspondence:
________________________________________ (National reference/European procedure number)
☑ A valid variation application has been received by the Competent Authority and where applicable by all Concerned Member States. Procedure start date is ________ Fees paid (for National use) ________
☑ Application invalid (reason) ___________________________________________________________
☑ Type I: The variation application cannot be accepted without amendment. The grounds for non-acceptance are notified below. Please respond by __________________________ (date)
☑ Type II: Supplementary information is requested as detailed below.
               Please respond by __________________________ (date)
☑ The Competent Authority consents to your request to vary the Marketing Authorization.
☑ The Competent Authority refuses your request to vary the Marketing Authorization (reasons below).

Signed __________________________ Date __________________________
Member State/Agency __________________________ Contact __________________________

NOTIFICATION WITH GROUNDS (TYPE I)/SUPPLEMENTARY INFORMATION (TYPE II)/REASONS FOR REFUSAL
**TYPE I CHANGES** (Tick against the appropriate change required)

<table>
<thead>
<tr>
<th></th>
<th>Change in the content of the manufacturing authorization</th>
<th>18.</th>
<th>Synthesis or recovery of non-pharmacopoeial excipients that had been described in the original dossier.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change in the name of the medicinal product (either invented name or common name)</td>
<td>19.</td>
<td>Change in specification of excipients in the medicinal product (excluding adjuvants for vaccines)</td>
</tr>
<tr>
<td></td>
<td>Change in the name and/or address of the marketing authorization holder</td>
<td>20.</td>
<td>Extension of shelf life as foreseen at time of authorisation</td>
</tr>
<tr>
<td></td>
<td>Replacement of an excipient with a comparable excipient (excluding adjuvants for vaccines &amp; biologically derived excipients)</td>
<td>21.</td>
<td>Change in shelf life after first opening</td>
</tr>
<tr>
<td></td>
<td>Deletion of a colorant or replacement of a colorant with another</td>
<td>22.</td>
<td>Change in shelf life after reconstitution</td>
</tr>
<tr>
<td></td>
<td>Addition, deletion or replacement of a flavour</td>
<td>23.</td>
<td>Change in the storage conditions</td>
</tr>
<tr>
<td></td>
<td>Change in coating weight of tablets or change in weight of capsule shells</td>
<td>24.</td>
<td>Change in test procedure of active substance *</td>
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<td></td>
<td>Change in the qualitative composition of immediate packaging material</td>
<td>25.</td>
<td>Change in test procedures of the medicinal product *</td>
</tr>
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<td></td>
<td>Deletion of an indication</td>
<td>26.</td>
<td>Changes comply with supplements to pharmacopoeias1</td>
</tr>
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<td></td>
<td>Deletion of a route of administration</td>
<td>27.</td>
<td>Change in test procedures of non-pharmacopoeial excipients</td>
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<td>Change in the manufacturer(s) of active substance *</td>
<td>28.</td>
<td>Change in test procedure of immediate packaging</td>
</tr>
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<td>Minor change of manufacturing process of the active substance *</td>
<td>29.</td>
<td>Change in test procedure of administration device</td>
</tr>
<tr>
<td></td>
<td>Batch size of active substance *</td>
<td>30.</td>
<td>Change in pack size for veterinary medicinal product *</td>
</tr>
<tr>
<td></td>
<td>Change in specifications of active substance *</td>
<td>31.</td>
<td>Change in container shape</td>
</tr>
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<td></td>
<td>Changes in manufacture of the medicinal product *</td>
<td>32.</td>
<td>Change of imprints, bossing or other markings (except scoring) on tablets or printing on capsules</td>
</tr>
<tr>
<td></td>
<td>Change in the batch size of finished product *</td>
<td>33.</td>
<td>Change of dimensions of tablets, capsules, suppositories or pessaries without change of quantitative composition and mean mass</td>
</tr>
<tr>
<td></td>
<td>Change in specification of the medicinal product *</td>
<td>34.</td>
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**TYPE II CHANGES** (Tick against the appropriate change required and detail the supporting data)

**A. Change to Part I dossier**

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**B. Change to Part II dossier**

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**C. Change to Part III dossier**

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**D. Change to Part IV dossier**

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State nature of change

(*) **Type I changes for which Type II procedure applies to products covered by the following**

(Tick the relevant box)

- Veterinary Immunological 90/677/EEC (*)
- Immunological 89/342/EEC (*)
- High Technology 87/22/EEC (List A) (*)
- Blood Product 89/381/EEC (*)
- Regulation (EC) 2309/93 Annex, Part A (*)

**MAIN CHANGE** (In case of consequential changes)

The main change covered by this variation application is change number/letter (1 to 33 / A to D)

---

1 If the reference in the dossier is to the 'current' edition of the pharmacopoeia, no notification is required, provided that the change is made within six months of adoption of the monograph.
Name of MA holder: ___________________________  Product name: ___________________________________
MA number/European procedure number: ___________________________________________

**RELATED APPLICATION(s)** (Please specify including date of pending renewal application(s))
__________________________________________________________________________________________________
__________________________________________________________________________________________________

**BACKGROUND** (Please give brief background explanation for the proposed changes to your MA)

(Specify the precise present and proposed wording or specification. For SPC and package leaflet/insert changes, underline or highlight the changed words and attach a complete new version.)

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<th>PROPOSED</th>
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I hereby make application for the above Marketing Authorization to be varied in accordance with the proposals given above and certify that the changes will not adversely affect the quality, efficacy or safety of the product. I declare that amended documents have been supplied and that the supporting information, where appropriate, meets the Type I conditions or supports the proposed Type II change. I declare that all changes have been identified and that there are no other changes in the amended documentation.

Fees paid (If applicable) Amount/ Currency __________________________________________________________

Please specify fee category under National/ Community rules ____________________________________________

**Main Signatory** ___________________________  Status (Job title) ___________________________

Print name ___________________________  Date ___________________________

**Second Signatory** ___________________________  Status (Job title) ___________________________

(Where appropriate)

Print name ___________________________  Date ___________________________

Please note that the application form is three (3) pages.
Appendix

FOR MUTUAL RECOGNITION PROCEDURE:
Name of MA holder: ____________________ Product name: ____________________
MA number/European Procedure number: ______________________________
Reference Member State: __________________ Other Concerned Member States: ____________

(For Official Use Only) RMS OR CMS TO COMPLETE SECTIONS AS INDICATED

Member State __________________ ______ Contact ____________________________

☐ (for RMS) A [ Type I ]/[ Type II ] (delete as appropriate) variation application was received on ________ (date). CMS to confirm receipt.

☐ (for CMS) A valid application was received on ____________ (date)
  □ Application invalid (reason) ______________________________
  □ The MA holder was informed of the reason on _________________ (date)
  □ A satisfactory response was received from the MA holder on __________ (date) and the application is valid

☐ (for CMS) A valid application has been received the RMS and all CMS. The procedure start date is ______________ (date)

TYPE I

☐ (for CMS) There are objective grounds for non-acceptance (reasons below). To reach RMS by Day 20 ____________ (date for completion by RMS)

☐ (for RMS) An amendment to the application has been received. The procedure re-start date is ____________ (date). Any objections to reach RMS by new Day 20 ____________ (date)

☐ (for CMS) Amendment from applicant has been considered.
  □ Variation acceptable ____________ (date) □ Variation not acceptable (reasons below)

☐ (for RMS) The variation and, where applicable, the amendment have been considered.
  □ Variation acceptable ____________ (date) □ Variation not acceptable (reasons below)

TYPE II

☐ (for RMS) A preliminary assessment report should be available by ____________ (date up to Day 40)

☐ (for RMS) A [preliminary] / [final] (delete as appropriate) assessment report is attached. Comments to be received from CMS by ____________ (date)

☐ (for CMS) The variation and assessment report have been considered.
  □ Conditions below on preliminary report only
  □ The conclusion of the assessment report is acceptable
  □ The conclusion of the assessment report is not acceptable (reasons below)

☐ (for RMS) State whether there is unanimous agreement on the conclusions of the assessment report:
  □ Yes. In the case of a positive decision the date of implementation will be ____________ (date)
  □ No. Arbitration procedures follow, referred to Agency on ____________ (date)

CONDITIONS FOR ACCEPTANCE / REASONS FOR NON-ACCEPTANCE

Signed __________________ Date __________________
Chapter 5  Variations

7. Completion of the application form

7.1 Purpose of the application form

The form is to be used for applications to vary Marketing Authorizations (Human and Veterinary) in accordance with Commission Regulations (EC) No. 542/95 (centralised) and No. 541/95 (mutual recognition). It can also be used for national Marketing Authorizations where the competent authorities within Member States have chosen to use the same form.

7.2 Application form – page 1

A human or veterinary medicinal product is indicated and whether the marketing authorisation (MA) is a Community authorisation (obtained through the centralised procedure) or a national authorisation (obtained using the mutual recognition procedure or on a national basis only). The variation, Type I or II (including urgent safety restriction), should be indicated.

For mutual recognition applications the Reference Member State (RMS) should be identified along with all Member States in which the product is authorized, that is the Concerned Member States (CMS). The abbreviations to be used are as follows:

- Austria  A T
- Belgium  BE
- Denmark  DK
- Finland  FI
- France   FR
- Germany  DE
- Greece   EL
- Ireland  IR
- Italy    IT
- Luxembourg  LU
- Netherlands  NL
- Portugal  PT
- Spain    ES
- Sweden  SE
- United Kingdom  UK

Full details of the marketing authorization should be included in respect of the product name (that is the invented or brand name), active substance/quantity (continue on a separate page if necessary), pharmaceutical form, the MA number and holder’s name and address. A contact person’s name within the company should be included together with a relevant address (if different from above), telephone and fax numbers. An E-mail number may be given.

The lower portion of the page is for Official Use and may be utilised by Member States as a communication page to the applicant with information concerning the progress of the
variation. It may also be used by Member States to convey the final decision to the applicant as to whether the variation is approved or refused. Additional information requested from the applicant or reasons for refusal will be indicated. Member States may alternatively choose to communicate with applicants by standard letters.

7.3 Application form - page 2

The different Type I categories are listed as they appear in the Regulations. The specific variation applied for should be indicated by ticking the appropriate box, and the number of volumes and pages of supporting data should be detailed.

A change may only be processed as a Type I variation if the condition to be fulfilled, as stated in Annex I of the Regulations, is satisfied. The European guidelines on Type I documentation should be consulted.

If the Type I conditions or data requirements cannot be fully satisfied this should be indicated under the background section on page 3 and a Type II variation should be applied for.

Type II approval procedures (that is the 90 day procedure) will apply for specific Type I categories (Type I changes for which a Type II procedure applies) in relation to the following products:

- within the scope of Directive 89/342/EEC
- 89/381/EEC
- 90/677/EEC

- which had been considered as arising under List A of Directive 87/22/EEC

- within the scope of Part A of the Annex to Council Regulation (EC) 2309/93 (centralised procedure)

Relevant products should be indicated on the form by ticking the appropriate box.

A Type II change should be indicated by ticking the appropriate box relating to the Part of the dossier to which the change applies (I - administrative/SPC; II - chemical/pharmaceutical/biological; III - pharmacotoxicological; IV - clinical). The nature of the change applied for should be stated as briefly as possible.

The supporting evidence should be detailed and an indication of whether an update or addendum to an expert report has been supplied. If an expert report is not currently available, for example in the case of older authorizations, the expert comment should address the specific change requested and the Addendum box should be ticked.

Consequential changes may be included on one application form but where more than one box is ticked (numbers 1 to 33, or letters A to D), the main change should be clearly indicated. Justification for the consequential nature of the additional changes should be given under the background section on page 3. If changes are not consequential a separate application form should be completed.
7.4 Application form - page 3

Details of the MA should be repeated to identify this page if used separately during Member States processing procedures. The RMS will add the European Procedure Number, as appropriate.

All related variation applications should be specified whether they are on the same MA or different MAs. The MA number, product and nature of variation should be included. If a renewal application is pending for the MA to which the variation applied for relates, the date of renewal application should be stated.

A brief background explanation should be given for the proposed change together with appropriate justification as required.

Applicants can assist in the assessment of the variation by summarising the present and proposed situations in the MA. Examples are attached to assist MA holders in completing this section. All differences should be clearly highlighted, eg italics, bold, underlined. If all the information cannot be fitted on this page, additional pages may be attached. For SPC and package leaflet/insert changes, copies of the existing version, highlighted version and new version should be provided.

The declaration needs to be signed and dated by a representative of the MA holder and the person’s name and job title should be printed to aid identification. Space is provided for a second signatory where a MA holder’s internal procedures or a Member State’s legal/administrative provisions require this facility. The minimum mandatory requirement remains as one signatory only.

Fees should be paid according to National/Community rules. The relevant fee category should be stated and a copy of the payment slip appended to the application, as appropriate.

7.5 Appendix

This page will be utilised by Member States for communication between the RMS and CMS in the mutual recognition procedure. Member States may alternatively choose to communicate by standard letters.

MA holders are requested to complete the details at the top of the page for variations in the mutual recognition procedure. The RMS will add the European Procedure Number.

7.6 Copies of form and data

Guidance is given in chapter VII of the number of copies of the completed application form and accompanying data, together with language requirements, required by Member States. For mutual recognition applications, the applicant should send one copy of the application form to the EMEA. A separate form should be completed for each Member State to take account of language requirements.

For identical changes to several presentations of a product, for example different strengths, one form must be completed for each MA. The RMS may use discretion to group applications, eg all strengths of a product, when using the Appendix to facilitate communication to Member States.

In the case that the space within the boxes on the application form is not sufficient, the required information should be submitted on separate pages attached.
8. Guideline on dossier requirements for Type I variations

In accordance with Regulation (EEC) No. 2309/93 and Directive 75/319/EEC as amended, a common approach to the procedures for variations to the terms of a marketing authorization have been identified. These procedures facilitate the task of both industry and authorities and also guarantee that changes to the medicinal product do not give rise to public health concerns.

Regulations (EEC) No. 541/95 and 542/95 set out the provisions relating to variations and categorised them into Type I and Type II.

For acceptance of a Type I variation documentation to demonstrate compliance with the conditions to be fulfilled must be submitted. In order to clarify what documentation should be submitted with these Type I variations, this guideline has been prepared. It elaborates the documentation required for both Regulation (EEC) No. 541/95 and Regulation (EEC) No. 542/95.

For each variation the relevant part of the dossier to be re-submitted or updated is identified, and any other documentation required also given. The appropriate fee must also be paid, in accordance with the prevailing rules at the time of submission.

Applicants should be aware that the Type I variation procedure sets out to provide for rapid and efficient processing of variations, and in that context, deficient or deviant documentation will necessitate a refusal of the variation. Refusals do not prejudice the applicant’s right to resubmission.
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<th>CONDITIONS/REMARKS</th>
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| 1. Change in the content of the manufacturing authorisation | The new manufacturing authorization, approved by the supervising competent authority, must be submitted to the competent authority. | - (See Annex for further information) New manufacturing authorisation (1) (this may be a new manufacturing authorisation, an addendum to the existing one, or a letter from the supervising competent authority) (2);  
- A revised package insert (for human medicines) and revised labelling (for veterinary medicines);  
- If other consequential variations apply, they must be applied for in accordance with the regulations. |

(1) The procedure for changing any of the particulars relating to the manufacturing authorisation is set out in Article 20 of Directive 75/319/EEC and Article 28 of Directive 81/851/EEC. The procedure for such changes shall not exceed 30 days; however, in exceptional cases this period may be extended to 90 days. Member States may require further information concerning the particulars supplied. In these cases the time limit shall be suspended until the additional data has been supplied.

(2) For vaccines, toxins, serums and allergens, medicinal products derived from human blood or plasma, immunological veterinary medicinal products and products derived from biotechnology, for which the manufacturing process is an intrinsic part of the quality of the product, any change to the manufacturing authorisation would generally entail further changes, such as change in batch size of the active substance (variation 13) or minor changes in the manufacture of the medicinal product (variation 15). Such further changes would be covered by the same application (i.e. a single fee). In the event that such a further change fell within the scope of variations 11, 12, 13, 14, 15, 16, 17, 24, 25 or 30, the procedure set out in Articles 6 and 7 apply i.e. 90 days with written approval. For chemically synthesised medicinal products, the specifications set out the quality of the product and therefore further variations would not always be necessary.
### Change in or of Conditions/Remarks

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| 2. Name of the medicinal product (either invented name or common name) | Confusion with names of other existing medicinal products or INN (international non-proprietary name) names must be avoided. When the name is a common name, the change has to be made in the following order: from common name to pharmacopoeial name or to INN. | - Revised drafts of the SPC, package leaflet/insert (1) and labelling incorporating the variation applied for;  
- Statement as to when the product will be marketed under the new name;  
- For a change of name required for a single market, the variation is submitted in all MS, although the change will only apply to that market. |
| 3. Name and/or address of the marketing authorization holder (see Art 4a of Directive 65/65/EEC or Art. 5a of Directive 81/851/EEC) | The marketing authorization holder shall remain the same person. | - Evidence that the MA holder remains the same;  
- Revised drafts of the SPC;  
- Statement as to when the change will be effective, with examples of package leaflet/insert (1) and labelling incorporating the variation applied for; |

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(1) The Directives use the term "package leaflet" for human medicinal products, where for veterinary products "package insert" is used.
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| 4. Replacement of an excipient with a comparable excipient (excluding adjuvants for vaccines and biologically derived excipients) | No change in dissolution profile for solid dosage forms. Same functional characteristics. | - Amendment to relevant sections of Parts II A, II B, II C and II E;  
- Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics (including stability aspect and antimicrobial preservation where appropriate);  
- Comparative dissolution profile data of at least one representative pilot/production batch of the finished product in the new and old composition for solid dosage forms;  
- Justification for not submitting a new bioequivalence study according to the current NfG "Investigation of Bioavailability and Bioequivalence";  
- Commitment that appropriate stability studies will be performed in accordance with the relevant stability guideline; data should be provided if outside specifications (with proposed action);  
- Revised drafts of the SPC (where applicable), package leaflet/insert (1) and labelling incorporating the variation applied for;  
- Declaration that the release and end-of-shelf life specifications of the finished product have not been changed;  
- Copy of approved release and end of shelf-life specifications;  
- For veterinary medicines, if the excipient has not previously been used in veterinary medicines for food producing species in the concerned member state(s), proof that the excipient is included in Annex II of the MRL Regulations 2377/90;  
- Data to demonstrate that the “new” excipient does not interfere with the finished product specification test method (if appropriate). |

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(1) The Directives use the term “package leaflet” for human medicinal products, where for veterinary products “package insert” is used.
### Chapter 5  Variations

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| 5. Deletion of a colorant or replacement of a colorant with another | | - Amendment to relevant sections of Parts II A, II B, II C (proposed colorant must be in accordance with Directive 78/25/EEC) and II E and should include identification method for the new colorant;  
- Revised drafts of the SPC (where applicable), package leaflet/insert (1) and labelling incorporating the variation applied for;  
- Sample of new product (see notice to applicants);  
- Commitment that appropriate stability studies will be performed in accordance with the relevant stability guideline; data should be provided if outside specifications (with proposed action);  
- Declaration that the release and end-of-shelf-life specifications have not been changed (except for appearance). |
| 6. Addition, deletion or replacement of a flavour | Proposed flavour must be in accordance with Directive 88/388/EEC. | - Amendment to relevant sections of Part II A, II B, II C and II E;  
- Amended sections of part ii c must contain details of qualitative composition of the flavour and any new specifications for the flavour. in case data on the flavour are submitted directly by the supplier of the flavour this data must be in the possession of the competent authority before the procedure can be started; name of supplier and the date of the submission of the data of the flavour must be stated in annex to the application;  
- Revised drafts of the SPC (where applicable), package leaflet/insert (1) and labelling incorporating the variation applied for;  
- Declaration that the release and end-of-shelf-life specifications of the product have not been changed (except for flavour);  
- Commitment that appropriate stability studies will be performed in accordance with the relevant stability guideline; data should be provided if outside specifications (with proposed action). |

(1) The Directives use the term “package leaflet” for human medicinal products, where for veterinary products “package insert” is used.
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<td>7. Change in coating weight of tablets or change in weight of capsule shells</td>
<td>No change in dissolution profile.</td>
<td>- Amendment to relevant sections of Parts II A, II B and II E; - Comparative dissolution profile data of at least one pilot/production batch of the finished product in the new and old composition (for modified release products using in vitro data which have been correlated with in vivo data); - Justification for not submitting a new bioequivalence study according to the current NfG “Investigation of Bioavailability and Bioequivalence”; - Declaration that the release and end-of-shelf-life specifications of the medicinal product have not been changed (except for average weight).</td>
</tr>
<tr>
<td>8. Qualitative composition of immediate packaging material</td>
<td>The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties. The change does not relate to sterile products.</td>
<td>- Amendment to relevant section of Part II A and II C; - Justification for the change in packaging material and appropriate scientific studies on the new packaging; - For semisolid and liquid dosage forms, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack); - Validation data must be given for all new analytical methods of the packaging material; - Comparative accelerated and real time stability data with previous packaging in accordance with the relevant stability guideline; - Declaration that the product will still meet the release and end-of-shelf life specifications of the product; - Revised SPC (where applicable), package leaflet/insert (1) and labelling incorporating the variation applied for.</td>
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(1) The Directives use the term “package leaflet” for human medicinal products, where for veterinary products “package insert” is used.
### Chapter 5  Variations

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| 9. Deletion of an indication                         | The continued safety in use of the medicinal product has not been the subject of concern from pharmacovigilance, preclinical safety or quality data. Justification must be given. | - Provision of reason for deletion of indication and declaration that no safety concerns exist for the product;  
- Revised draft of the SPC;  
- Statement as to when the change will be effective with examples of the package leaflet/insert \(^1\) and labelling (where applicable) incorporating the variation applied for. |
| 10. Deletion of a route of administration            | The continued safety in use of the medicinal product has not been the subject of concern from pharmacovigilance, preclinical safety or quality data. Justification must be given. | - Provision of reason for deletion of route of administration and declaration that no safety concerns exist for the product;  
- Revised draft of the SPC;  
- Statement as to when the change will be effective with examples of the package leaflet/insert \(^1\) and labelling (where applicable) incorporating the variation applied for. |
| 11. (2) Manufacturer(s) of active substance          | The specifications, synthetic route and quality control procedures are the same as those already approved or a European pharmacopoeia certificate of suitability covering the active substance is submitted. | - Amendment to relevant sections of Part II C;  
- Batch analysis data of at least two batches (minimum pilot scale);  
- A declaration from the marketing authorisation holder that the synthetic route, quality control procedures and specifications are the same as those already approved;  
or Ph. Eur. certificate of suitability,  
or a new DMF \(^3\);  
Where the change relates only to the name of the manufacturer of the active substance, a statement as to when the change will become effective. |

\(^1\) The Directives use the term “package leaflet” for human medicinal products, where for veterinary products “package insert” is used.

\(^2\) For products consisting of vaccines, toxins, serums and allergens or derived from human blood or human plasma and for biotech products which have been considered as arising under List A of Directive 87/22/EEC or under Part A of the Annex to Regulation (EEC) 2309/93 the procedure for a Type II variation is applicable.

\(^3\) Submission of the new DMF in advance will facilitate the procedure; see also the document “Use of EDMF procedure”.  

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Chapter 5   Variations

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<td>12. (1) Minor change of manufacturing process of the active substance</td>
<td>Specifications not adversely affected.  No change in the physical properties.  No new impurities or change in level of impurities which would require further qualifications in safety studies.</td>
<td>- Amendment to relevant section of Part II C including a direct comparison of the present process and the new process;  - Batch analysis data of at least two batches (minimum pilot scale);  - Evidence must be provided that any potential new impurities are detectable at an acceptable limit of detection; declaration that no new impurities have been introduced or that there is no increase in the level of impurities, which require further safety studies;  - Validation data must be provided for all new analytical methods (where applicable) (see also variation 24);  - Declaration that the specifications of the active substance have not been changed (see also variation 14) or if there is any change to the specifications, the texts of the current and proposed specifications should be provided (side by side comparison where possible);  - Copy of approved specifications of the active substance.</td>
</tr>
<tr>
<td>13. (1) Batch size of active substance</td>
<td>Batch data must show that the change does not affect consistency of production, or physical properties.</td>
<td>- Amendment to relevant section of Part II C;  - Batch analysis data (in a comparative tabulated format) on a minimum of one production batch manufactured to both the currently approved and the proposed sizes. Batch data on the next 2 full production batches should be available on request or reported if outside specification (with proposed action);  - Declaration that the specifications of the active substance have not been changed;  - Copy of approved specifications of the active substance;  - Evidence must be provided that any additional potential impurities are detectable at an acceptable unit of detection.</td>
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(1) For products consisting of vaccines, toxins, serums and allergens or derived from human blood or human plasma and for biotech products which have been considered as arising under List A of Directive 87/22/EEC or under Part A of the Annex to Regulation (EEC) 2309/93 the procedure for a Type II variation is applicable.
### Chapter 5 Variations

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| 14. (1) Change in specifications of active substance. | Specifications must be tightened or addition of new test and limits. | - Amendment to relevant section of Part II C;  
- Validation data must be provided for all new analytical methods (where applicable) (see also variation 24);  
- Comparative dissolution profile data for the finished product (if appropriate) on at least one pilot production batch containing the active substance complying with the current and proposed specifications;  
- Comparative batch analysis data covering all tests in the specifications for at least 2 pilot/production batches;  
- Comparative list of old and new specifications of active substance. |
| 15. (1) Minor changes in manufacture of the medicinal product. | Medicinal product specifications are not adversely affected. New process must lead to an identical product regarding all aspects of quality, safety and efficacy. | - Amendment to relevant sections of Part II B which contains:  
  - for semisolid and liquid products in which the active substance is present in non dissolved form appropriate validation of the change including microscopic imaging of particles to check for visible changes in size distribution and morphology;  
  - for solid dosage forms dissolution profile data of 1 representative production batch and comparative data of the last 3 batches from the previous process. data on the next 2 full production batches should be available on request or reported if outside specification (with proposed action);  
  - Declaration that the release and end-of-shelf life specifications of the product have not been changed or if there is any change to the specifications, the texts of the current and proposed specifications should be provided (side by side comparison where possible);  
  - Justification for not submitting a new bioequivalence study according to the current NIG “Investigation of Bioavailability and Bioequivalence”;  
  - Copy of approved release and end-of-shelf-life specifications;  
  - In case of change to a sterilisation process, justification and validation should be provided. |

(1) For products consisting of vaccines, toxins, serums and allergens or derived from human blood or human plasma and for biotech products which have been considered as arising under List A of Directive 87/22/EEC or under Part A of the Annex to Regulation (EEC) 2309/93 the procedure for a Type II variation is applicable.
## Chapter 5 Variations

<table>
<thead>
<tr>
<th>CHANGE IN OR OF</th>
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<th>DOCUMENTATION TO BE SUPPLIED</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. (1) Batch size of finished product.</td>
<td>The change does not affect consistency of production.</td>
<td>- Amendment to relevant sections of Part II B;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Batch analysis data (in a comparative tabulated format) on a minimum of production batch manufactured to both the currently approved and the proposed batch sizes, batch data on the next 2 full production batches should be available on request or reported if outside specifications (with proposed action);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Declaration that the release and end-of-shelf life specifications of the product have not been changed;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Copy of approved release and end-of-shelf-life specifications.</td>
</tr>
<tr>
<td>17. (1) Change in specification of the</td>
<td>Specifications must be tightened or addition of new tests and limits.</td>
<td></td>
</tr>
<tr>
<td>medicinal product</td>
<td></td>
<td>- Amendment to relevant section of Part II E;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Validation data must be provided for all new analytical methods;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Comparative dissolution profile where appropriate;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Comparative batch analysis data covering all tests in the specification for at least 2 production scale batches;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Comparative listing of old and new release and end of shelf-life specifications of the product.</td>
</tr>
<tr>
<td>18. Synthesis/recovery of non-</td>
<td>Specifications are not adversely affected. No new impurities or change in level of</td>
<td></td>
</tr>
<tr>
<td>pharmacopoeial excipients which had</td>
<td>impurities which would require further qualification in safety studies.</td>
<td></td>
</tr>
<tr>
<td>been described in the original dossier</td>
<td>No change in physico-chemical properties.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Amendment to relevant sections of Part II C which contain appropriate validation data;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Comparative batch analysis data of at least two batches;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Declaration that the specifications of excipients have not been changed or if there is any change to the excipient specifications, the texts of the current and proposed specifications should be provided (side by side comparison where possible);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Declaration that no new impurities have been introduced or that there is no increase in the level of impurities, which require further safety studies.</td>
</tr>
</tbody>
</table>

(1) For products consisting of vaccines, toxins, serums and allergens or derived from human blood or human plasma and for biotech products which have been considered as arising under List A of Directive 87/22/EEC or under Part A of the Annex to Regulation (EEC) 2309/93 the procedure for a Type II variation is applicable.
### Chapter 5 Variations

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| 19. Change in specification of excipients in the medicinal product (excluding adjuvants for vaccines) | Specifications must be tightened or addition of new tests and limits. | - Amendment to relevant section of Part II C;  
- Validation data must be provided for all new analytical methods (see also variation 27);  
- Comparative dissolution profile data of at least one pilot/production batch of the finished product, if appropriate;  
- Justification for not submitting a new bioequivalence study according to the current NFG “Investigation of Bioavailability and Bioequivalence”;  
- Comparative batch analysis data covering all tests in the specification for at least 2 pilot/production batches of the finished product;  
- Comparative list of old and new specifications of the excipients. |
| 20. Extension of shelf-life as foreseen at time of authorisation. | Stability studies have been done to the protocol which was approved at the time of the issue of the marketing authorisation. The studies must show that the agreed end-of-shelf-life specifications are still met.  
The shelf-life does not exceed five years. | - Amendment to relevant sections of Part II F must contain results of appropriate stability studies (tabulated format) of the product in the authorized packaging material in accordance with the relevant stability guideline;  
- Revised drafts of the SPC (where applicable), package leaflet/insert (1) and labelling incorporating the variation applied for;  
- Declaration that the end-of-shelf-life specifications of the product have not been changed and that the product will still meet these specifications;  
- Copy of approved end-of-shelf-life specifications;  
- Declaration that the additional stability studies have been done to the protocol which was approved at the time of issue of the marketing authorisation and that the agreed end-of-shelf-life specifications are still met. |

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(1) The Directives use the term “package leaflet” for human medicinal products, where for veterinary products “package insert” is used.
<table>
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| 21. Change in shelf-life after first opening | Studies must show that the agreed end-of-shelf-life specifications are still met. | - Amendment to relevant sections of Part II F must contain results of appropriate stability studies of the product in the authorised packaging material in accordance with the relevant stability guideline; where applicable, results of appropriate microbiological testing should be included;  
  - Revised drafts of the SPC (where applicable), package leaflet/insert (1) and labelling incorporating the variation applied for;  
  - Declaration that the specifications of the product after first opening have not been changed and that the product will still meet these specifications;  
  - Copy of approved end-of-shelf-life specification;  
  - Declaration that the additional stability studies show that the agreed end-of-shelf-life specifications are still met. |
| 22. Change in shelf-life after reconstitution | Studies must show that the agreed end-of-shelf-life specifications are still met for the reconstituted product. | - Amendment to relevant sections of Part II F must contain results of appropriate stability studies of the product in the authorized packaging material in accordance with the relevant stability guideline; where applicable, results of appropriate microbiological testing should be included;  
  - Revised drafts of the SPC (where applicable), package leaflet/insert (1) and labelling incorporating the variation applied for;  
  - Declaration that the specifications of the product after reconstitution have not been changed and that the product will still meet these specifications.  
  - Copy of approved end-of-shelf-life specification;  
  - Declaration that the additional studies show that the agreed end-of-shelf-life specifications are still met for the reconstituted product. |

(1) The Directives use the term “package leaflet” for human medicinal products, where for veterinary products “package insert” is used.
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<tr>
<td>23. Storage conditions</td>
<td>Stability studies have been done to the protocol which was approved at the time of issue of the marketing authorisation. The studies must show that the agreed end-of-shelf-life specifications are still met.</td>
<td>- Revised drafts of the SPC (where applicable), package leaflet/insert (1) and labelling incorporating the variation applied for;</td>
</tr>
<tr>
<td>24.2 Change in test procedure of active substance</td>
<td>Results of method validation show new test procedure to be at least equivalent to the former procedure.</td>
<td>- Amendment to relevant sections of Part II C which includes validation data and comparative analytical results between the current test and the new one, if appropriate;</td>
</tr>
<tr>
<td>25.2 Change in test procedures of the medicinal product</td>
<td>Medicinal product specifications are not adversely affected. Results of method validation show new test procedure to be at least equivalent to the former procedure.</td>
<td>- Amendment to relevant sections of Part II E and/or Part II F which includes validation data and comparative analytical results between the current test and the new one, if appropriate;</td>
</tr>
</tbody>
</table>

(1) The Directives use the term “package leaflet” for human medicinal products, where for veterinary products “package insert” is used.

(2) For products consisting of vaccines, toxins, serums and allergens or derived from human blood or human plasma and for biotech products which have been considered as arising under List A of Directive 87/22/EEC or under Part A of the Annex to Regulation (EEC) 2309/93 the procedure for a Type II variation is applicable.
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| 26. Changes to comply with supplements to pharmacopoeias. (In cases where the marketing authorization refers to the current edition of the pharmacopoeia, no notification is required provided the change is introduced within six months of adoption of the revised monograph.) | Change is made exclusively to implement the new provisions of the supplement. | - Amendments to appropriate parts of Part II;  
- Active substances: when changing from a non-EU pharmacopoeia or from company specifications documentation should be provided to demonstrate the suitability of the new monograph in the European Pharmacopoeia or national pharmacopoeia of the Member State to control the substance from that particular manufacturer. This may be done for example by:  
  • comparing a list of potential impurities in the substance with the transparency note of the monograph;  
  • providing a Ph. Eur. certificate; In case the new Ph. Eur. specification or national pharmacopoeia of the member state of active substances or excipients may affect the quality of the finished product, comparative batch analysis data covering all tests in the finished product specification for at least 2 production scale batches should be provided together with comparative dissolution profile where appropriate;  
- Finished products: in case of a new general monograph (on dosage form) or a new general requirement a single application may be submitted for a list of products covered by the new monograph/requirement, unless the new requirement calls for product specific validation. |
| 27. Test procedures of non-pharmacopoeial excipients | Results of method validation show new test procedure to be at least equivalent to the former test procedure. | - Amendment to relevant sections of Part II C which includes analytical validation data; comparative analytical validation data should be provided with the existing method;  
- Declaration that the specifications of the excipients have not been changed. |
| 28. Test procedure of immediate packaging | Results of method validation show new test procedure to be at least equivalent to the former test procedure. | - Amendment to relevant sections of Part II C which include analytical validation data; comparative analytical validation data should be provided with the existing method, where appropriate;  
- Declaration that the specifications of the immediate packaging have not been changed. |
<table>
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| 29. Test procedure of administration device | Results of method validation show new test procedure to be at least equivalent to the former procedure. | - Amendments to relevant sections of Part II C which include validation data; comparative validation data should be provided with the existing method, where appropriate;  
- Reference to CEN standard and/or CE marking for device where applicable;  
- Declaration that the specifications of the administration device have not been changed. |
| 30. Change in pack size for a veterinary medicinal product | Specifications of the medicinal product are not affected, the new size is consistent with the dosage regimen and duration of use as approved in the SPC.  
The change does not relate to parenteral preparations. | - Declaration that the specifications of the medicinal product are not affected, that the new size is consistent with the dosage regimen and that the duration of use is as approved in the SPC;  
- Revised drafts of the SPC, package insert and labelling incorporating the variation applied for;  
- Declaration that the container and closure composition is unchanged and in the case of plastics, an assurance that the polymer wall thickness is at least as thick as the current packs;  
- Declaration that stability studies will be conducted for products where physical properties could be affected e.g. suspensions. Results to be reported if outside specification (with proposed action). |
| 31. Change in container shape | No change in the quality and in the stability of the product in the container.  
No change in the container-product interactions. | - Amendment to relevant sections of Part II C3 (including a detailed drawing of the previous and new forms) if applicable;  
- Samples of old and new containers (see NTA, requirement for samples in the member states);  
- Declaration that the specifications of the container (except for shape) have not been changed;  
- Declaration that the release and end-of-shelf life specifications of the product have not been changed. |

(1) For products consisting of vaccines, toxins, serums and allergens or derived from human blood or human plasma and for biotech products which have been considered as arising under List A of Directive 87/22/EEC or under Part A of the Annex to Regulation (EEC) 2309/93 the procedure for a Type II variation is applicable.
### Chapter 5 Variations

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| 32. Change of imprints, bossing or other markings (except scoring) on tablets or printing on capsules | New markings do not cause confusion with other tablets or capsules. | - Amendment to relevant sections of Part II B and II E (including a detailed drawing or written description of the previous and new situation);  
- Samples of the finished product (see NTA, requirement for samples in the Member States);  
- Declaration that the release and end-of-shelf life specifications of the product have not been changed (except for appearance);  
- Revised drafts of the SPC (where applicable), package leaflet/insert (1) and labelling incorporating the variation applied for. |
| 33. Change of dimensions of tablets, capsules, suppositories or pessaries without change of quantitative composition and mean mass | No change in dissolution profile. | - Amendment to relevant sections of Part II B and II E (including a detailed drawing of the previous and new situation);  
- Comparative dissolution data on at least one pilot/production batch of the current and proposed dimensions;  
- Declaration that the release and end-of-shelf life specifications of the product have not been changed (except for dimensions);  
- Revised drafts of the SPC (where applicable), package leaflet/insert (1) and labelling incorporating the variation applied for;  
- Samples of the old and new product.  
- Data of breakability test of tablets at release must be given and commitment to submit data of breakability at the end of shelf-life. |

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(1) The Directives use the term “package leaflet” for human medicinal products, where for veterinary products “package insert” is used.
9. Type II variation applications (V) versus new applications (NA)

A Guideline on the categorisation of TYPE II VARIATION APPLICATIONS (V) VERSUS NEW APPLICATIONS (NA) has been prepared in order to facilitate the operation of the procedures for variations. Whilst comments and contributions on this text may be made, nonetheless the categorisation set out in this text may be used, from 1.6.97, for applications through the either mutual recognition procedure or the centralised procedure.

For the practical application of the Annex II of the Regulations (EEC) 541/95 and 542/95 concerning the classification of new applications versus type II variations, particular difficulties appeared regarding the items **strength and pharmaceutical form**.

However based on results of a questionnaire and using the European Pharmacopoeia document “STANDARD TERMS Pharmaceutical dosage forms - Routes of administration - Containers - Special issue October 1996” as a reference, the principles described below have been agreed. In this document, the pharmaceutical form is defined as a combination of the form in which the product is presented by the manufacturer (form of presentation) and the form in which it is administered (form of administration). It is also stated that in certain cases a complete characterisation of the pharmaceutical form requires additional information about the container. This applies in any case to prefilled syringes, pressurised preparations and single-dose preparations. It applies also in cases where the administration of the same physical form differs due to a different design of the container/administration device (e.g. pressurised container versus spray pump).

It should be emphasized that the classification has been agreed for the purposes of centralised and mutual recognition procedures and it has no implication for administration of fees, marketing authorization number etc.

9.1 Definitions and principles

1. **Strength and concentration**
   
   1) For solid forms, **strength** is defined as the amount of active substance per unit dose;
   
   2) For liquids ready-to-use preparations, the strength is identical to the **concentration**;
   
   3) For powder for reconstitution (powder for oral solution, powder for injection etc.) the strength is identical to the **concentration after reconstitution** to the volume recommended.

2. **Single dose container**

   Products which are specially designed as single-dose preparations (according to Standard Terms) are classified as specific pharmaceutical forms. These preparations will often, but not always, have a different composition regarding excipients (e.g. preservatives) than the equivalent **multi-dose container**: single dose is refered to only when multi-dose forms exists.

   Examples: sachets; eye drops.
3. **Use on one occasion**

Although it is difficult to make a distinction between single dose and single use, a pragmatic approach was developed using the terminology already provided by the document Standard Terms.

To avoid any confusion, it has been agreed that **single dose** is different from **single use** which means that the content is intended for use on one occasion only (e.g. ampoules, vials).

4. **Different administration devices**

Pressurised container and spray pump are classified as individual pharmaceutical forms as mentioned in Standard Terms.

5. **Addition of a strength or pharmaceutical form**

The same classification is applied to both a replacement and an addition of a strength or pharmaceutical form.

**Examples**

A number of examples where the above mentioned principles are implemented are listed below using the following abbreviations:

- NA: New application
- V: Variation (Type II)

**9.2 Oral preparations**

1. **Oral preparation - solid**

1.1 different pack size, same strength, same immediate packaging (e.g. pack of 16 tablets vs pack of 24 tablets) => V

1.2 different immediate packaging, same strength, same pack size (e.g. blister of 16 tablets vs container of 16 tablets) => V

1.3 different strength (e.g. tablet of 200 mg vs tablet of 500 mg) => NA

2. **Oral preparation - liquid**

2.1 liquid preparation ready to use at the same concentration

2.1.1 different size of immediate packaging, same concentration (e.g. bottle of 100 ml vs bottle of 200 ml) => V

2.1.2 multidose vs single dose, same concentration (e.g. bottle of 100 ml vs sachet of 10 ml) => NA

2.2 powder for oral solution

2.2.1 multidose vs single dose, same concentration after reconstitution (e.g. bottle of 100 g vs sachet of 1 g) => NA

2.2.2 different concentration after reconstitution (e.g. 50 mg/ml vs 100 mg/ml after reconstitution) => NA
9.3 Parenteral preparations

1 Small volume of parenteral preparation

1.1 vial vs pre-filled syringe same volume, same concentration => NA
1.2 vial vs pre-filled syringe but only for the solvent => NA
1.3 ampoule vs vial same volume, same concentration => V
1.4 different volume, same concentration (e.g. vial of 5 ml vs vial of 1 ml) => V
1.5 multidose vs single dose, same concentration (e.g. vaccines...) => NA
1.6 different concentration (for powders, after reconstitution) => NA
1.7 different size of immediate packaging, same concentration after reconstitution (vial of 1ml vs vial of 5ml for the same concentration of 1mg/ml) => V

2 High volume of parenteral preparation (clinical nutrition, NACL 0,9%, glucose 5%...)

2.1 different type of immediate packaging, same volume, same concentration (e.g. plastic bag vs glass vial) => V
2.2 different size of immediate packaging, same concentration (e.g. plastic bag of 1 l vs plastic bag of 5 l) => V
2.3 different concentration (e.g. 10% vs 5%) => NA

9.4 Preparations for inhalation

1. Solution, emulsion, suspension, for inhalation

1.1 addition, deletion or change of medical device, (e.g. spacer) => V
1.2 different immediate packaging (as defined in the standard terms guideline) (e.g. spray pump vs pressurised container) => NA
1.2 different concentration, same immediate packaging (e.g. 5 mg/puff vs 10 mg/puff) => NA

2. Powder for inhalation

2.1 addition, deletion or change of medical device (e.g. spacer) => V
2.2 different immediate packaging (e.g. inhalation powder in disc vs inhalation powder in hard capsule) (as defined in Standard Terms) => NA
2.3 different strength (e.g. 2 mg/hard capsule vs 1 mg/hard capsule) => NA

3. Change of propellant (new propellant has fulfilled toxicological etc requirements)

3.1 new propellant, same active substance, same (other) excipients => V
3.2 new propellant: different content per actuation or dosing schedule or a quantitative change in the active substance(s) or a change in bioavailability => NA
9.5 Local preparations

1. **Cutaneous preparations**
   1.1 addition, deletion or change of medical device (same concentration) => V
   1.2 different immediate packaging, same strength or concentration (e.g. jar vs tube) => V
   1.3 same immediate packaging, same strength or concentration but different volume (e.g. tube of 5 g vs tube of 10 g) => V
   1.4 different strength or different concentration (e.g. 1 g/100 g vs 2 g/100 g) => NA

2. **Eye preparations**
   2.1 multidose vs single dose, same concentration (e.g. multidose of 5 ml vs single dose of 1 ml for eye drops) => NA
   2.2 same immediate packaging but different size, same concentration (e.g. multidose of 5 ml vs multidose of 10 ml or single dose of 0.5 ml vs single dose of 1 ml ) => V
   2.3 different concentration (e.g. 1 g/10 ml vs 2 g/10 ml) => NA

9.6 Rectal or vaginal use

1. **Suppository, capsule, tampon for vaginal or rectal use, ovule for vaginal use...**
   1.1 addition, deletion or change of medical device, same strength => V
   1.2 different pack size (e.g. pack of 16 suppositories vs pack of 24 suppositories) => V
   1.3 different strength (e.g. 100 mg/suppository vs 200 mg/suppository) => NA
   1.4 multidose vs single dose, same strength (e.g. tube 10 g vs sachet 1 g) => NA

2. **Cream, gel, ointment, foam, solution, emulsion, suspension for vaginal use or rectal use**
   2.1 addition, deletion or change of medical device (same concentration) => V
   2.2 different size of immediate packaging, same concentration (e.g. bottle of 60 ml vs bottle of 120 ml) => V
   2.3 multidose vs single dose, same concentration => NA

3. **Powder for rectal or vaginal solution, suspension**
   3.1 different strength or different concentration after reconstitution => NA
   3.2 multidose vs single dose, same strength or same concentration after reconstitution (e.g. bottle of 100 g vs sachet of 5 g) => NA
ANNEX

Variation Type I, Number 1

Change in the content of the Manufacturing Authorisation

In Directive 75/318/EEC as amended by Directive 91/507/EEC, the applicant is required to annex to the administrative data (Part IA of the dossier) copies of the manufacturing authorisation as defined in article 16 of Directive 75/319/EEC.

Article 16 of Directive 75/319/EEC requires that an authorisation to manufacture or import medicinal products is required for
- total or partial manufacture (including contractor);
- processes of dividing up, packaging or presentation;
- imports coming from third countries.

Further, article 17 of Directive 75/319/EEC establishes the content of a manufacturing authorisation as, at least
- the manufacturing authorisation holder;
- specification of the medicinal products and pharmaceutical forms;
- place of manufacture and/or control.

The Commission’s Inspectors working party are currently considering a harmonised presentation of the manufacturing authorisation and may well include annexes to the manufacturing authorisation.

A variation application (Type I, number 1) is required when the information relating to the content of the manufacturing authorisation (the manufacturing authorisation holder; specification of the medicinal products and pharmaceutical forms; place of manufacture and/or control) for the medicinal product concerned is changed.