Variation applications within the European Community for a) innovative medicinal Products authorised by centralised procedure b) new medicinal products authorised by mutual recognition procedure

Wissenschaftliche Prüfungsarbeit

Zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

Vorgelegt von

Sandra Maria Strobl

aus München

Bonn 2002

Betreuer und erster Referent: Wolfram Gering

Zweiter Referent: Dr. Bettina Bettauer

Table of Contents ***page***

A Introduction

Innovative medicinal products as defined in Part B of Annex of Regulation 2309/93/EEC may optionally be granted via centralised procedure. Whereas, all medicinal products containing new substances as described under Chapter 4, Volume II of the NtA (except products for the centralised procedure) shall be granted via national (mutual recognition) procedure.

In accordance with Directive 65/65/EEC, as amended by Directive 2001/83/EC for human medicinal products [1], and 81/851/EEC for veterinary medicinal products a marketing authorisation is valid for a period of five years. The authorisation is renewable at least three months before the expiry date.
Once a marketing authorisation has been issued by the competent authority the marketing authorisation holder's interest shall lie in keeping his product on the market without scarifying the public health.
Quality, safety and efficacy can only be maintained by consequent updates for reasons of scientific and technical progress or by adding or changing the safety information.
Commitments or requests by the competent authority still to be fulfilled after an approval or the renewal may lead to a change of the product information.
Marketing authorisation holders may also wish to add changes to their licence by improving or altering their medicinal product.
In addition, from the marketing point of view and based on bench marketing results the wish of competitiveness of companies' products and scientific knowledge may lead to improvement and changes to marketing authorisations.

For innovative medicinal products first approved via centralised procedure and for such as new medicinal products first approved via Mutual Recognition Procedure there is given the regulatory need to maintain the achieved harmonisation.
With respect to the different needs of changes or <variations> on the medicinal product the regulators laid down in two regulations the respective actions to be done.
Two types of variations are classified. These may cover administrative and/or more substantial changes.

Therefore, in the following variation applications within the European Community for innovative medicinal Products authorised by centralised procedure as well as new medicinal products authorised by mutual recognition procedure are discussed.

B Legal basis and purpose

The examination of minor and major variations is applicable for Mutual Recognition Procedures (MRP) and Centralised procedures.
Basis for the application of variations to the terms of a marketing authorisation are the Commission Regulations 541/95/EC [8] (as amended by 1146/98/EC) for MRP and 542/95/EC [10] (as amended by 1069/98/EC) for centralised procedures. They are cross-referring to the respective Directives and Regulations relevant to ensure efficient and clear understanding and interpretation of the processes.

Both regulations are applicable for medicinal products for human and veterinary use.
They are explained in more detail by guidelines and notices released for MRP and centralised procedures. Nevertheless, it has to be considered when reading those texts that are not legally binding that the legal requirements of the Directives and Regulations must be met.
In the following paragraphs and sections of this document each relevant reference is mentioned.

C List of Abbreviations

AR	Assessment Report
CMS	Concerned Member State(s)
CPMP	Committee for Proprietary Medicinal Products
CTD	Common Technical Document
DDL	Dear Doctor Letter
EMEA	European Agency for the Evaluation of Medicinal Products
ER	Expert Report
EU	European Union
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MAA	Marketing Authorisation Application
MRFG	Mutual Recognition Facilitation Group
MS	Member State(s)
NCE	New Chemical Entity
PVAR	Preliminary Variation Assessment Report
FVAR	Final Variation Assessment Report
PIL	Package Information Leaflet
PhVWP	Pharmacovigilance Working Party
RAS	Rapid Alert System
RMS	Reference Member State
RSI	Request for supplementary information
SmPC	Summary of Product Characteristics
USR	Urgent Safety Restriction

D Changes to a marketing authorisation

Taking into account the different needs of changes to a Marketing Authorisation (MA) the MAH has to demonstrate compliance with the regulatory conditions to be fulfilled.

After an authorization has been issued in accordance with the respective regulation, based on new experiences the person responsible for placing a medicinal product on the market has to ensure and to adopt continuously quality, safety and efficacy of the product.

With respect to the methods of production and control provided for as set out in article 8 of Directive 2001/83/EC [1], the MAH has to consider any technical and scientific progress and shall make any amendments that may be required to enable the medicinal products to be manufactured and checked by means of generally accepted scientific methods.

As the granting of authorization does not diminish the general civil and criminal liability (Directive 2001/83/EC, Art. 25 [1]) the MAH has forthwith to inform all relevant competent authorities of any safety relevant information which might entail an amendment of the respective documents, for instance the approved summary of product characteristics. Any prohibition or restriction imposed by the competent authorities of any country have to be communicated which might influence the evaluation of the benefits and risks of the medicinal product concerned. The aforementioned person has to apply for approval for these amendments in accordance with the respective Regulation.

Such changes or 'variations' may apply for national (mutual recognition) and community (centralised) procedures.
Administrative and/or more substantial changes and procedures which require an approval are set out in the two Commission Variation Regulations (541/95/EC [8] and 542/95/EC[10] as amended respectively).
In both regulations the following Types of Variations are defined:

- Type I Variation (minor variation, notification procedure)
- Type II Variation (major variation, approval procedure)

Changes, which may lead to a Type I variation, are listed in Annex I to Regulation 541/95/EC [8] and 542/95´/EC [10], as amended. Changes which are not listed in Annex I of these Regulations require a Type II variation.
Changes, which fundamentally alter the MA can not be considered as a variation. A new application has to be applied for. In Annex II of both regulations the respective changes are set out. The product name in this new application has to be changed accordingly. Normally the name of a medicinal product remains unchanged except for major changes of e.g. serious risks to public health. Here the competent authority may also require a different name.

Therefore, in case of urgent Safety Restrictions USR the MAH has to react promptly within 24 hours. The MAH is obliged to submit a type II variation without any delay imposing all relevant changes for the evaluation of the benefits and risks of a human or veterinary medicinal product.

To be sure of the correct procedure and the Type of variation the MAH has to define first the changes based on the relevant Variation Regulation. Guidelines help in defining and categorising the variation Type and the documents to be submitted. The categorisation of Type II variations versus new applications is described in a separate Guideline [3].
For variations to the terms of a MA through MRP the Mutual Recognition Facilitation Group releases helpful guides/SOPs/recommendations to facilitate such procedures and to avoid arbitrations.

Each application should contain only one variation. If several variations are made each application shall contain reference to the other application. A variation, which entails one or more further changes, the relation between the main and the consequential variation(s) shall be described.
This is valid for Type I and Type II variations in national and community procedures as set out in the Regulations 541/95/EC [8] and 542/95/EC [10], as amended.

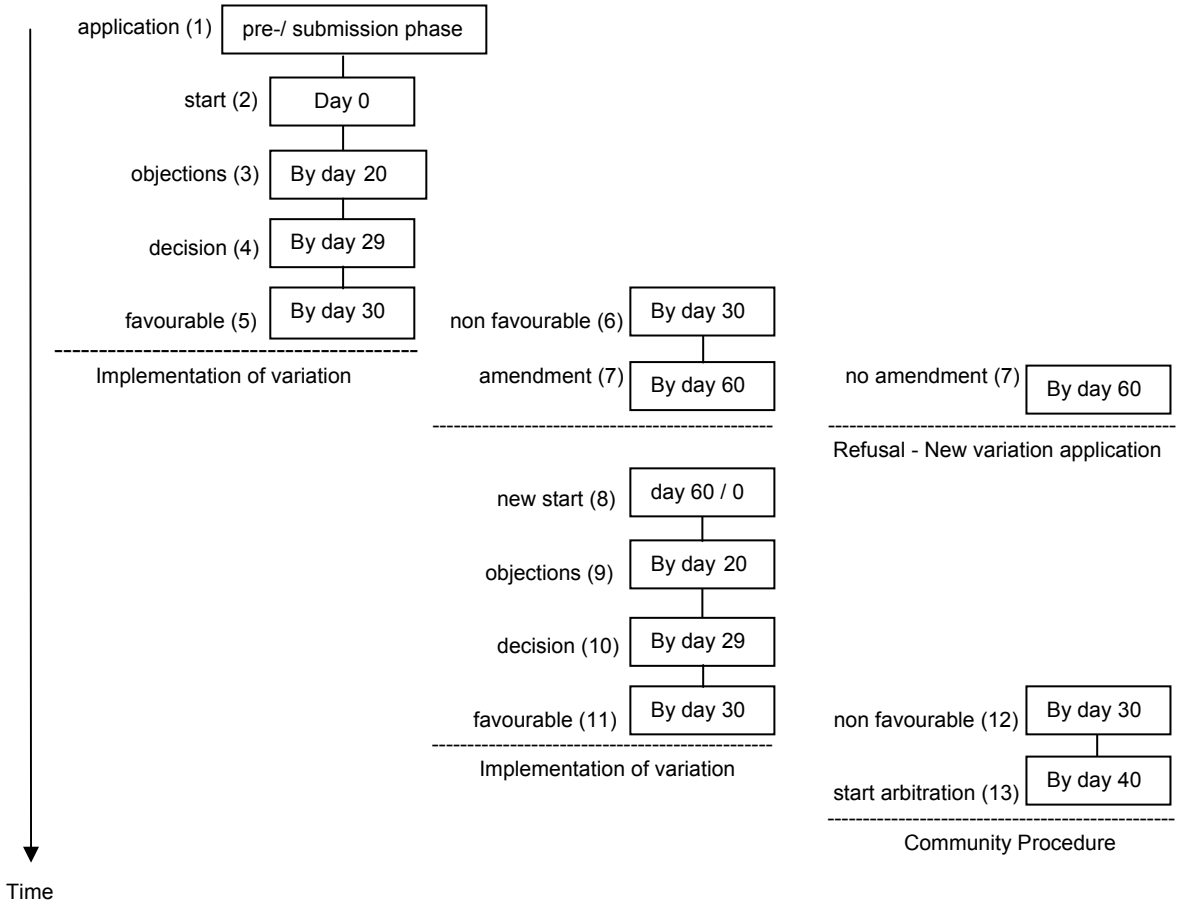
E Procedures
1. Mutual Recognition Procedure

After first approval of an application in a MRP the AR has been updated and Eudratrack is completed.
To make a variation the MAH has to apply for a variation first. Harmonised data and identical SmPCs are submitted simultaneously in all MS concerned and adopted to national requirements, fees and correct number of copies. Package information leaflets may be adopted nationally after approval.
The following operational scheme is a guide when processing variations. Notes by the NtA are not highlighted. The regulation 541/95/EC is directly binding and describes relevant actions of the procedures to be done for centralised and Mutual Recognition procedures. All these are pointed out in blue. Additional comments made by the MRFG are presented in lilac.

1.1 Type I variation

Based on the regulation 541/95/EC [8] the Marketing Authorisation Holder has to ensure that the conditions for the Type I variation are met and all requirements as stated in the guideline <A Guideline on dossier requirements for Type I variations, November 1999 [4]> are fulfilled. The current EC application form should be used (see also Appendix 1). Correct completion of this form is one of the preconditions of a successful validation in the first steps of the procedure.

1.1.1 Time scales



1.1.2 Actions to be taken by applicant, CMS and RMS

NOTE:
The middle column (regulation) of the following chart is focussing all relevant information, which describe Type I procedures. These have been described in more detail in the guideline of the NtA and by the MRFG. Only the additional recommendations to the regulation are shown in the left and right column given by the NtA and MRFG.

Steps MRP Type I	Notice to Applicants (Volume IIA, Chapter 5/7) [13]	Regulation 541/95/EC [8]	MRFG [5] [6] [7] [12]
(1) Application	**Applicant** • EC application form should be used. • One week prior to the intended submission date submission to the RMS to obtain the respective variation number. • Then, after having received this number an identical application with the variation number completed on the application form shall be submitted simultaneously to all CMS in which the authorisation of the medicinal product is given. Different national requirements or deviations from the guideline pointing out <dossier requirements for Type I variations> [4] should be considered. • Corresponding changes on the SmPC, label and/or label/insert have to be highlighted. • Correct amount of fees should be despatched. • The MAH should ensure the correct number of copies of the application form and supportive data laid down in Annex I of the Regulation 541/95/EC [8] in appropriate languages of each Member State (RMS, CMS) concerned. For the correct languages and number of copies see also Chapter VII of Volume 2A of the NtA. • When despatch is completed to all Member States concerned a fax should be sent to all stating the despatch dates of the variation application with the product name. • One copy of the application form should be sent to the EMEA. • Sample requirements for Type I variations see also Chapter VII of Volume 2A of the NtA (if applicable the sample has to be provided upon request within 7 calendar days).	**Applicant** • An identical application should be submitted simultaneously to all MS concerned where the medicinal product is authorised. Based on Annex I of this regulation all relevant documents to fulfil the conditions have to be provided. • There should be a list indicating all CMS and the RMS. • All data and documents supporting the variation application as outlined under Annex I of regulation 541/95 shall be submitted. • All fees based on national regulations have to be paid accompanying the application.	

Steps MRP Type I	Notice to Applicants (Volume IIA, Chapter 5/7) [13]	Regulation 541/95/EC [8]	MRFG [5] [6] [7] [12]
..(1) Application	**CMS** • As soon as the variation application is received validation of completeness of sent documents is made. If there are deficiencies during validation or missing data the RMS should be informed about the reason for delay. A copy has to be sent to the MAH. In case such problems occur after fixed start day (day 0) this issue has to be raised on day 20. **RMS** • After having received the documents the variation application has to be identified and the variation number is assigned within one week. • Validation for completeness and correctness of the application has to be performed (fee, application form, Type I conditions fulfilled, supporting data, amended documents, justification for consequential variations).		**CMS** • They are not obliged to inform the RMS of the receipt of the application (Contrary to the NtA). **RMS** • The variation application should be entered into Eudratrack. Record will be completed.
(2) Start	**RMS** • Only the RMS is actually required to inform about the start. • This is day 0.	**RMS** • Notifies the applicant and CMS about the procedure start date.	
(3) Objections	**CMS** • Any objections to the variation should be addressed to the RMS including grounds for an invalid validation notified after the clock start day 0. **RMS** • Objections have to be reviewed.	**CMS** • Notifies/Notify the RMS about any ground for objection.	
(4) Decision	**RMS** • If there are objections by the CMS and/or by the RMS, the RMS will make a decision and take the necessary action. Only the RMS is required to notify the CMS and the applicant about the decision.		

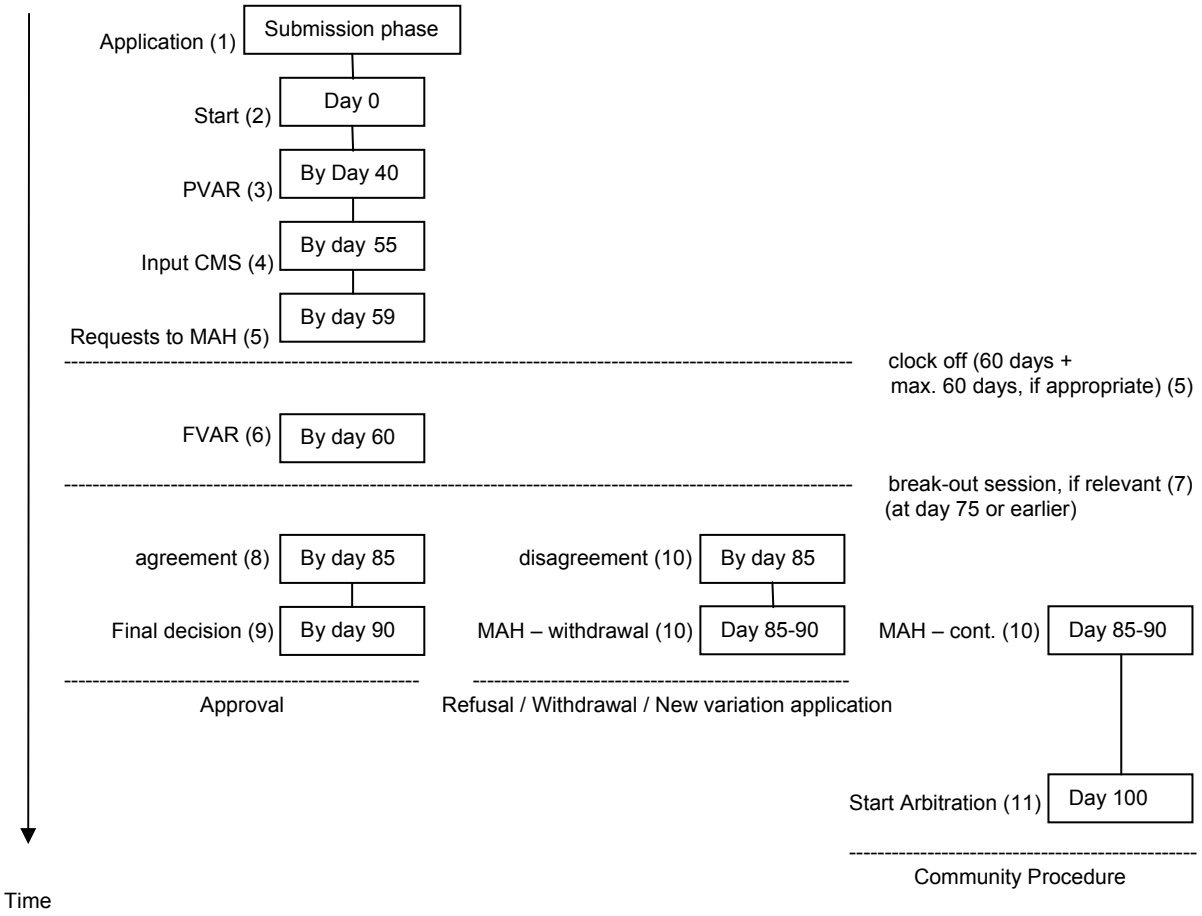
Steps MRP Type I	Notice to Applicants (Volume IIA, Chapter 5/7) [13]	Regulation 541/95/EC [8]	MRFG [5] [6] [7] [12]
(5) Favourable	**Applicant** • The variation has to be implemented. As the time period of implementation may vary nationally the requirements have to be checked accordingly with each MS concerned. **RMS** • The applicant and CMS may be notified of acceptance of the variation application. This is not requested if no objections within 30 days occurred.	**RMS** • If within 30 days the RMS does not respond to the application the variation can be deemed to be accepted.	
(6) Non favourable	**RMS** • Reasons for non-acceptance of the variation are notified to the CMS and applicant. • Advice should be given to the applicant.	**RMS** • Within 30 days the RMS has to inform the MAH about the grounds for non-acceptance.	
(7) Amendment	**Applicant** • Revisions on SPC/label/insert should be highlighted. • Again the correct number of copies of the amendment in appropriate language/s should be submitted. The applicant has to assure that all the documents supporting the amendment are sent to all MS concerned. • Consequently a completely new variation application has to be applied for. **RMS** • If the amendment is not submitted within the requested time period the application is refused on day 60. This formal action is actually done only by the RMS, on behalf of all CMS.	**Applicant** • Within 30 days of receipt of the reasons for non-acceptance the applicant may provide the RMS and CMS simultaneously with new and/or revised documents to take due account of the grounds set out in the notification. • There is only one occasion for an amendment of documents justifying the variation application. • All applications have to be modified in the same sense. **RMS** • If the applicant does not pursue the request to respond accordingly the application is refused. The rejection is valid for all member states concerned. MAH and all CMS are informed accordingly.	

Steps MRP Type I	Notice to Applicants (Volume IIA, Chapter 5/7) [13]	Regulation 541/95/EC [8]	MRFG [5] [6] [7] [12]
(8) New start	**CMS** • The CMS inform(s) RMS and applicant in case of non receipt of the amendment. **RMS** • The RMS will notify applicant and CMS of the new start day. Clock will only stop if the CMS inform(s) about non receipt of the amended application.		
(9) Objections	**CMS** • Any objections to the revised variation application should be addressed to the RMS. **RMS** • All objections have to be reviewed and discussed with CMS, as necessary.		
(10) Decision	**RMS** • Based on the amended application the RMS will make the decision.		
(11) Favourable	**Applicant** • The variation has to be implemented. • The time period of implementation has to be considered for each MS concerned. **RMS** • The applicant and CMS are notified of acceptance of the variation application.		
(12) Non favourable	**RMS** • It indicates whether the decisions of the MS are divergent.	**RMS** • A formal refusal should be notified forthwith to the applicant and all CMS.	
(13) Arbitration	**Applicant** • For procedure see section 1.2.4. All member states concerned are involved. The procedure itself and the decision is made on Community level.	**Applicant** • Within ten days the applicant may refer this matter for arbitration to the Agency. This is only applicable if the rejection is based on divergent decisions of the member states concerned.	

1.2 Type II variation

To ensure an appropriate variation application and to fulfil the requirements MAH, CMS and RMS have to base their actions on the Regulation 541/95/EC [8]. Guidelines as the NtA, Vol. 2A [13] and supporting papers released by the MRFG [5] [6] [7] [12] should be considered. It is useful to follow the given advice of the Mutual Recognition Facilitating Group in order to facilitate applications in MRP. Its main target is to speed up the procedures including variations by supporting efficient dialog between all MS concerned maintaining mutual recognition and avoiding time consuming arbitration procedures.

1.2.1 Time scales



1.2.2 Actions to be taken by applicant, CMS and RMS

NOTE:
The middle column (regulation) of the following chart is focussing all relevant information, which describe Type I procedures. These have been described in more detail in the guideline of the NtA and by the MRFG. Only the additional recommendations to the regulation are shown in the left and right column given by the NtA and MRFG.

Steps MRPType II	Notice to Applicants (Volume IIA, Chapter 5/7) [13]	Regulation 541/95/EC [8]	MRFG [5] [6] [7] [12]
(1) Application	**Applicant** • The applicant has to ensure that the criteria for a new application are not fulfilled, i.e. the variation is classified as a type II variation according to the <guideline on the categorisation of new applications (NA) versus variation applications> [3]. • It is recommended that changes on SmPC/label or insert are highlighted. • The EU application form should be used. • Before submitting the variation application to all CMS the applicant should send a draft of the application form to the RMS to get the variation procedure number. Additional documentation should be provided if necessary. • Simultaneous submission of all supporting documents has to be done. Appropriate languages of submitting documents should be ensured. In parallel a copy of the application form should be sent to the Agency. • The correct amount of copies in each MS has to be provided (see also NtA, Vol 2A, Chapter 7) • The applicant has to confirm the application stating the dates of submission in all member states concerned and that the fees are paid. • If within 7 days the CMS did not send a copy of confirmation of the receipt of the variation application the MAH has to investigate the reasons. • Sample requirements see NtA, Vol 2A, Chapter 7.	**Applicant** • As laid down in the regulation 541/95/EC all data supporting the variation application have to be provided. All relevant documents have to be amended with reference to those to be substituted. Additionally, the corresponding expert report has to be revised and presented as an addendum or update. • A list of all member states concerned should be included. • All fees based on national regulations have to be paid accompanying the application.	**Applicant** • The applicant has to discuss the timetable with the RMS keeping in mind a flexible starting day in order to match a potential break out session with the MRFG at day 75. Overlapping procedures should be avoided.

Steps MRPType II	Notice to Applicants (Volume IIA, Chapter 5/7) [13]	Regulation 541/95/EC [8]	MRFG [5] [6] [7] [12]
..(1) Application	**CMS** • The CMS have to validate the variation application. If there are some inconsistencies or missing documents the RMS should be informed immediately about the reasons for delay. At the same time the MAH should be informed by sending a copy. • The RMS is informed about the validity of the application. • A copy of the valid application is sent to the applicant. **RMS** • The RMS should discuss the timetable with the MAH ensuring an efficient variation process in a timely manner. • The variation application has to be validated. • The variation European Procedure Number has to be provided to all CMS. • In case of non receipt in one or several CMS the RMS is informed and has to check the reasons.	**CMS** • The CMS has to inform the RMS about the receipt and completeness of the application	**CMS** • If the MAH has provided the supplementary missing information the respective CMS has to inform the RMS within 5 working days about the validity. **RMS** • The RMS has to give the applicant the procedure number. • As soon as the variation application has been received the Eudratrack should be updated. Validation has to be done (automatic procedure). • If after 5 working days the RMS did not receive all confirmations of receipt the RMS may start within the next 5 working days unless it is notified about any invalidity.
(2) Start	**RMS** • Only the RMS is actually required to inform applicant and CMS about the start date. • The RMS will inform the CMS up to when the PVAR can be expected.	**RMS** • The RMS has to determine the start day and will inform all CMS and the MAH.	**RMS** • The clock can be started 10 days after confirming letter by the applicant of submission of the variation application unless the notification of an invalid application is received. In exceptional cases and where necessary the timelines may be modified to accelerate the variation procedure. Agreement between RMS and CMS must be ensured.

Steps MRPType II	Notice to Applicants (Volume IIA, Chapter 5/7) [13]	Regulation 541/95/EC [8]	MRFG [5] [6] [7] [12]
(3) PVAR		**RMS** • Within 60 days an assessment report with a draft decision has to be circulated to all CMS.	**RMS** • The PVAR is sent also to the MAH. At this stage this report should be regarded by the MAH as information only. • Any delay of the report has to be communicated to the CMS. • A clear statement whether the application can be accepted or not should be included. RSI only makes sense if the deficiencies do not exceed a certain limit. Otherwise this will lead to a refusal. • If changes on the SmPC are not accepted the RMS has to propose an alternative version acceptable with recently approved similar products via the MRP.
(4) Input CMS	**CMS** • A clear opinion on the PVAR has to be given stating whether approval is acceptable or not. Also a statement to the RSI is desired.		**CMS** • Grounds for non-acceptance should clearly be indicated by communicating requests for supplementary information from the MAH. Proposals for SmPC changes may be given but kept to a minimum. The CMS should focus the proposals presented by the RMS. • Any matter not focusing directly the variation application is not appropriate. • If the CMS sends no comments the RMS can regard this behaviour as agreement to the PVAR.
(5) Requests to MAH – clock off	**Applicant** • If by day 59 RMS and CMS could not agree to the proposed variation application the clock-off period will start. • Within 60 days the applicant has to submit simultaneously all requested supplementary information to the RMS and all CMS. • This period for provision of additional information may be extended for further 60 days agreed with the RMS. • Revised SPC/label/leaflet have to be provided as well.	**Applicant** • The RMS will send a single RSI to the applicant. All CMS are informed accordingly. • The 60 days period may be extended for a period determined by the competent authority or upon request of the MAH.	**Applicant** • If the applicant is not able to respond appropriate it is recommended to withdraw the application. • A new variation application may be applied for.

Steps MRPType II	Notice to Applicants (Volume IIA, Chapter 5/7) [13]	Regulation 541/95/EC [8]	MRFG [5] [6] [7] [12]
..(5) Requests to MAH – clock off	**CMS** • A copy of RSI is sent to the CMS, if appropriate. • The MAH will provide the CMS with appropriate supplementary information as requested. **RMS** • It is the responsibility of the RMS that the RSI may be sent to the MAH, if appropriate. A copy of the RSI will be sent to the CMS. • Any objection raised by the CMS will be considered. • Time span for response will be discussed with the MAH. The 60 days clock off for response may be prolonged for generally not more than additional 60 days in exceptional cases only.		**RMS** • Reasons for prolongation of the time period for response of the MAH for additional 60 days are generally communicated to the CMS.
(6) FVAR	**CMS** • The CMS receive(s) the FVAR for comments from the RMS.	**RMS** • The variation assessment report with a draft decision is prepared and sent to all CMS.	**Applicant** • The MAH may receive the FVAR at day 60. **RMS** • The FVAR and revised SPC are circulated to all CMS for comments (day 60, clock-restart). • Additionally, a revised SmPC with all relevant sections shall be attached for review. • The RMS will make arrangements to release the FVAR to the MAH.
(7) Break-out session (for objective and details of this process see section 1.2.3)			**RMS/CMS/EMEA/Applicant** • In case of disagreement of safety concerns between RMS and CMS such a meeting may be arranged. It is to achieve a mutual recognition/consensus and to clarify divergent decisions. Timing of a meeting may be kept flexible. RMS and EMEA co-ordinate the arrangements for a break-out meeting.

Steps MRPType II	Notice to Applicants (Volume IIA, Chapter 5/7) [13]	Regulation 541/95/EC [8]	MRFG [5] [6] [7] [12]
(8) Agreement	**CMS** • If by day 85 there is a positive harmonised agreement between all CMS involved in the final decision the RMS is informed about the acceptance.	**CMS/RMS** • Within 30 days following the draft decision and the assessment report by the RMS, the CMS inform the RMS about their acceptance. • The decision has to be adopted in each CMS, which will take effect on the day agreed with the RMS and the MAH.	
(9) Final decision	**Applicant** • By day 90 the MAH will be informed about the date of approval. **CMS** • All CMS are informed about the formal approval. **RMS** • On or before day 90 formal approval has to be notified to all CMS and the applicant.		**Applicant** • The revised and approved SPC may not be changed except a new variation procedure is applied for. Within 10 working days of the approval date the MAH is obliged to provide all CMS with the new SmPC in national languages, respectively. **RMS** • The completion of the procedure will be notified and the date of the finalisation is communicated (also via e-mail) to the applicant and CMS on day 90 at the latest. • The final affected sections of the SmPC will be circulated. • The MAH is informed about the following steps to provide all relevant translations in national languages within 10 working days. **RMS/CMS** • Within 30 days after receiving the respective SmPC/PIL/labelling in national languages the decision of the approval should be nationally implemented. Eudratrack and MR Product Index have to be maintained and continuously updated throughout procedure.

Steps MRPType II	Notice to Applicants (Volume IIA, Chapter 5/7) [13]	Regulation 541/95/EC [8]	MRFG [5] [6] [7] [12]
(10) Disagreement – MAH withdrawal – MAH cont.	**Applicant** • If no agreement between all MS can be achieved or a refusal is likely the MAH may withdraw the application from all MS. • The variation may be withdrawn in all MS concerned not later than initiation of an arbitration procedure. Once the referral has been triggered the MAH may still withdraw but only in all MS concerned. **RMS/CMS** • If there is a negative but harmonised agreement between all MS involved in the final decision the variation application may be refused. **RMS** • If divergent positions between MS remain or a refusal is likely the RMS will contact the MAH recommending withdrawal. Any other decision and its effective date is notified by the RMS to all CMS and the applicant.	**RMS/CMS** • If no agreement between the MS can be achieved (between day 60 and 90) Article 15, last paragraph, Directive 75/319/EEC or Article 23, last paragraph, of Directive 81/851/EEC shall apply.	**Applicant** • If no agreement between all MS can be achieved even in the break out session the MAH may withdraw from all MS. **RMS/CMS** • Even in the break out session the matter (divergent positions) is taken into binding arbitration. Those member states which can't agree on the final proposal and draft decision by the RMS have to make the formal referral to arbitration. If only the RMS can't accept the proposal from the MAH, the RMS has to refer this matter to arbitration. The CPMP/CVMP and the MAH have to be informed in each case, accordingly.
(11) Start Arbitration (see 1.2.4)			**Applicant** • A complete dossier should be provided to the EMEA.

1.2.3 Break-out session

The MRFG released a Paper 'Best Practice Guide on Break-out sessions' [5].

Type II variations mean major changes. This may lead to divergent decisions between all MS concerned and the RMS. To facilitate discussions of serious risks to public health concerns and to achieve a consensus and harmonised SmPC the MRFG offers the possibility to discuss such issues on Community level.
To facilitate the communication between the MS video or tele-conferencing facilities may be used. The EMEA MRFG Secretariat will be informed accordingly.
Representatives from all CMS including the MAH are invited to the plenary MRFG meeting. Interested MS not involved in that variation and also non-EU countries may attend that meeting as observers. The RMS will chair the meeting.
A maximum of 5 experts authorised to make decisions from the MAH may participate to answer remaining questions. A proposed list shall be sent to the RMS and the EMEA MRFG Secretariat.

The exact timing of a break-out session may depend on urgency, individual situation and issue. Based on the PVAR, on the RSI or the resulting comments from the CMS in relation to the next MRFG meeting the RMS shall schedule a meeting and timetable confirmed by the EMEA.

After a discussion focussing the still outstanding issues the applicant may be asked to join the meeting. As the time is limited a well-prepared and clearly defined strategy and questions may support a positive course of the procedure. Still remaining issues will be discussed after departure of the applicant, with the objective to reach final consensus and a harmonised SmPC.

A brief report prepared by the RMS should summarise the grounds and outcomes of the discussion. All parties involved and concerned should receive a copy of it.

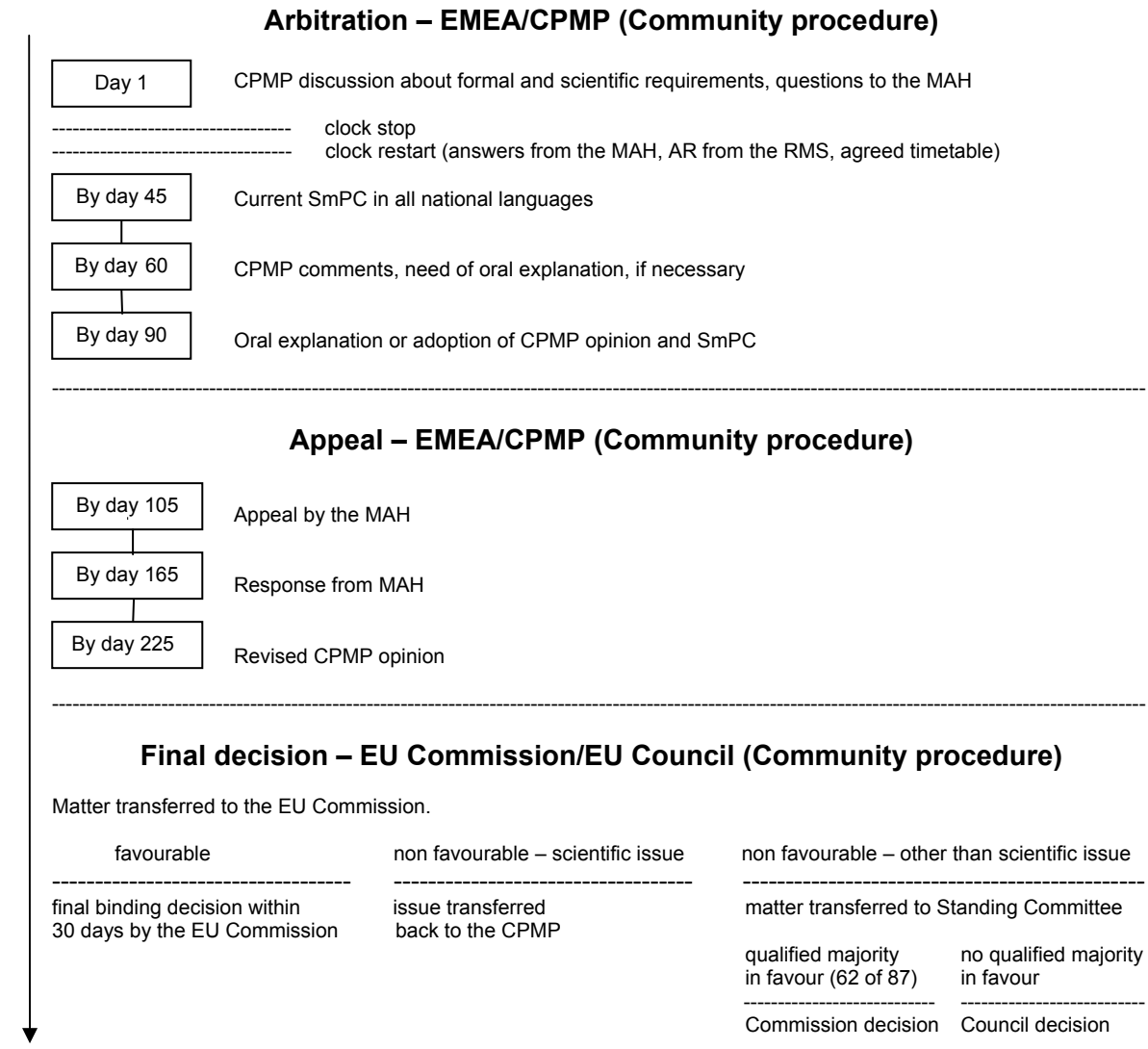
1.2.4 Arbitration (only by serious objections – risk to public health)

If a variation leads to arbitration for protection of public health the matter is referred to a Community procedure. The EMEA is then provided with a complete variation application dossier. Respective fees have to be paid as set out in Council Regulation 297/95/EC [9]. The appeal procedure as described under the centralised procedure could be used by the applicant to appeal against a CPMP opinion resulting from an arbitration procedure.
In the period from day 55 to 90 of the variation procedure discussions between RMS and CMS will primary concentrate on risks to public health.
The only reason for rejection of Mutual Recognition is the risk to public health. Rejections concerning the SmPC are based on the following issues only:

- Indication
- Posology and method of administration
- Contraindications
- Special warnings and precautions for use
- Shelf-life and storage requirements

Whenever in the event of disagreement between member states about quality, safety or efficacy of the medicinal product, which has not been resolved by day 90, an arbitration is being invoked, scientific evaluation will be undertaken by the EMEA's CPMP leading to a final opinion.

The final decision is made by the European Commission or if necessary by the Council which is then binding for the MAH and all MS concerned. At the end of the referral procedure a single harmonised Summary of Product Characteristics is issued. Within 30 days the final binding decision has to be transferred in all MS concerned.
The legal procedure of arbitration for variations is based on Article 15 and set out in Article 13 and 14 of Directive 75/319/EEC [2]. In Chapter 3 and 6 of Vol. 2 of the NtA [13] the procedure is described in more detail.
All fees and upcoming costs have to be paid by the MAH. All relevant and supporting documents have to be supplied.
The following flow chart will give a rough overview about that Community procedure.



1.2.5 Urgent Safety Restriction

A type II variation may also be triggered by an urgent safety restriction (USR) in the event of risk to public or animal health. Relevant sections of the SmPC will have to be revised accordingly. Information exchange should be performed via the Rapid Alert System (RAS) [15].

Irrespective of national or Community procedure an USR may lead to restrictions in indications, posology and/or patients treated. Adding of contraindications or warnings may also be a consequence of an USR for protection of public health.

According to the MRFG an urgent safety restriction (USR) can be divided in three phases: before, during and after the 24-hour urgent safety restriction period. A respective paper released by the MRFG describes the process as follows [12].

BEFORE the USR:
The MAH or a member state can initiate an USR.
If the MAH initiates the process (or confirms the USR request of the RMS) the RMS has to be supplied with all necessary information and a timetable should be agreed about the public communication and regulatory action to be taken.
If a MS initiates an USR a consensus between MS and RMS has to be reached about this issue. Then the MAH will be involved to proceed the procedure.
If a consensus between MS and RMS about an USR is not possible the PhVWP tries to achieve this. In case no consensus can be achieved, national actions can be imposed to the MAH.
Disagreement of the MAH about the USR requested by the RMS leads to a revised SmPC proposed by the RMS itself. The RMS starts the 24-hour period.

DURING the 24-hour Urgent Safety Restriction period:
The MAH submits information to RMS and CMS (=start of 24-hour period) containing:
submission form, all available information relating this issue, proposed revised SPC and if applicable proposed revised package leaflet, Dear Doctor letter (DDL) and investigation letter.
During the 24-hours period the member states can raise proposals relating to the USR; the RMS finally decides which of them are adopted (24-hour period relates to working days, i.e. Saturdays, Sundays and public holidays are excluded).

AFTER the USR:
The RMS informs about the final outcome.
The MAH submits translation of SPC and DDL within 24 hours and has to initiate a type II variation not later than 15 days after completion of the 24-hour USR period.

The national authorities are free to impose own national actions (press release, batch recall or suspension/withdrawal of marketing authorisation) if they consider it necessary to protect the public health.

2 Centralised Procedure

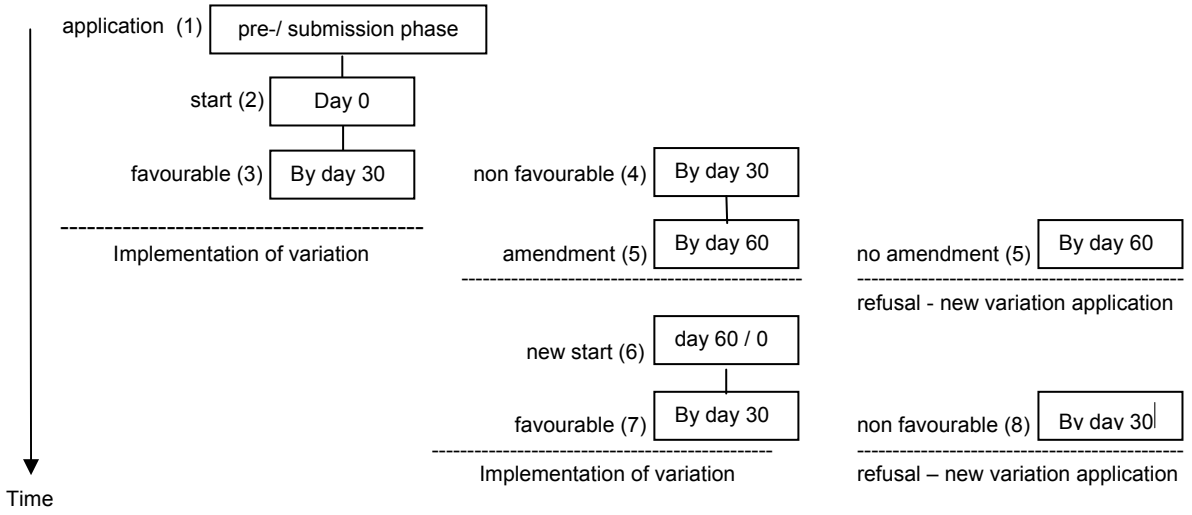
Innovative medicinal products may be granted under the centralised procedure as set out in Council Regulation 2309/93/EEC [11].
The procedures of variations to a marketing authorisation are set out in Regulation 542/95/EC [10]. In this regulation two types of regulation are defined.
Based of this regulation marketing authorisations may be amended. All relevant documents as pointed out in Guideline <Dossier Requirements for Type I variations> [4] have to be provided.
Exceptions in which a Type I is performed as Type II variation, however, fee for Type I variations has to be paid are mentioned under Annex I of the latter regulation.

In the following paragraphs the procedures for both types of variations are described in detail. If appropriate, revised labelling and Package inserts have to be presented in accordance with Council Directive 92/27/EEC [1].

2.1 Type I variation

The procedure of minor variations is described in Regulation 542/95/EC [10].

2.1.1 Time scales



2.1.2 Actions to be taken by applicant, EMEA/CPMP

NOTE:
The right column of the following chart is focussing all relevant and binding actions for Type I procedures described in regulation 542/95/EC. These have been described in more detail in the guideline of the NtA. Only the additional recommendations given by the NtA to the regulation are shown in the left column.

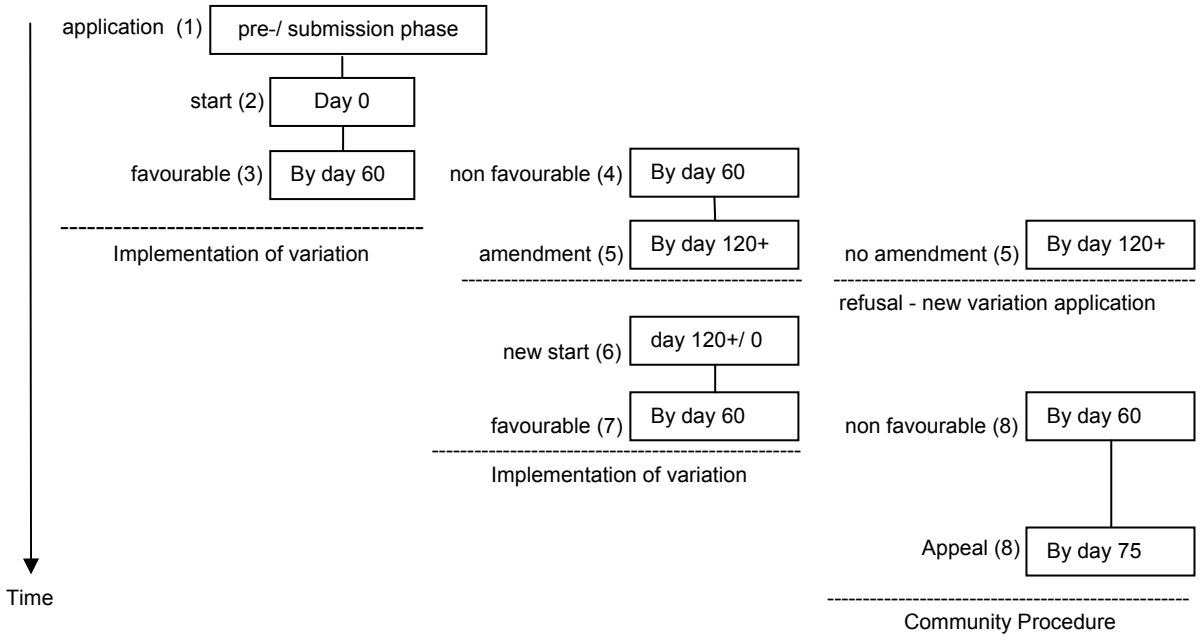
Steps Centralised Type I	Notice to Applicants (Volume IIA, Chapter 5) [13]	Regulation 542/95/EC [10]
(1) Application	**Applicant** • The intention to apply for a variation has to be communicated to the EMEA. At least one month prior the intended date for submission the strategy and, if relevant, Co-/Rapporteur are determined. • It has to be ensured that all relevant documents including a justification for the type of variation can be enclosed to the EU application form. • Reference to those documents to be substituted from the original dossier should be given. • If appropriate, amendments in all official languages to be introduced in the Commission decision should be provided. • Changes on the SmPC, label and/or label/insert have to be highlighted. • The MAH should ensure that the correct languages and number of copies are provided. For correct languages and number of copies see also Chapter VII of Volume 2A of NtA. • Sample requirements see NtA, Vol2, Chapter 7 (samples are generally not required at time of submission, however, for testing during procedure they may be requested). **EMEA/CPMP** • Once the applicant has informed the EMEA Secretariat about the intention to apply for a Type I variation a project manager is appointed. • Rapporteur and Co-Rapporteur may be nominated. In general both remain the same as those for the evaluation of the application of the marketing authorisation in the centralised procedure. In case of transfer of a MA a new Co-/Rapporteur may be appointed. • Timelines and strategy will be defined. • After submission the validation of the application is done within 5 working days.	**Applicant** • The MAH has to ensure that the application from and the supportive documentation as laid down in Annex I of the Regulation 542/95/EC are supplied. • The relevant fee as laid down in Regulation 597/95/EC has to be provided.
(2) Start	**Applicant** • The applicant is informed about the start of the procedure. **EMEA/CPMP** • Once validated the clock starts. Applicant, Co-/Rapporteur and other CPMP members will be informed accordingly.	

Steps Centralised Type I	Notice to Applicants (Volume IIA, Chapter 5) [13]	Regulation 542/95/EC [10]
(3) Favourable		**Applicant** • If within 30 days the applicant is not informed by the Agency the changes of the variation applied for are deemed to be accepted and may be implemented. **EMEA/CPMP** • The Agency is not requested to reply within 30 days. • Within those 30 days the Agency shall inform the European Commission about the variation. **EU Commission** • Within 30 days after having received the favourable opinion by the EMEA the EU Commission shall release its final decision as laid down in Article 10 of Regulation 2309/93/EEC [11]. The Community register will be updated as necessary (Article 12, 2309/93/EEC [11]).
(4) Non favourable		**EMEA/CPMP** • The Agency has to inform the applicant in case it is of the opinion that the application made by the applicant may not be accepted. The Agency has to notify the MAH about the objections. • The Commission is informed accordingly. **EU Commission** • The draft decision by the EU Commission may be different compared to the positive opinion from the Agency. • For making the final decision in the variation procedure Article 10 as laid down in Regulation 2309/93/EEC applies (see also 1.2.4). If the decision is not favourable this is communicated to the EMEA and the MAH stating all grounds for rejection. • The final decision shall take effect retroactively to the day of the opinion notified by the EMEA.
(5) Amendment	**Applicant** • Revisions on SPC/label/insert should be highlighted. The correct languages and amount of copies should be provided. • The rejection is valid for all member states. Consequently a completely new variation application has to be applied for. **EMEA/CPMP** • If no amendment is submitted within 30 days the variation is rejected in all EU member states.	**Applicant** • Based on the objections and the grounds delivered by the Agency the MAH may amend its application within 30 days. • If the applicant does not pursue the request to respond accordingly the application is rejected.

Steps Centralised Type I	**Notice to Applicants (Volume IIA, Chapter 5) [13]**	**Regulation 542/95/EC [10]**
(6) New Start	*see (2)*	*see (2)*
(7) Favourable	*see (3)*	*see (3)*
(8) Non favourable	**Applicant** • The Applicant has to apply for a new variation. **EMEA/CPMP/EU Commission** • If the Agency and/or EU Commission cannot agree to the amendment to the variation application the application is rejected. This is communicated to the EMEA and the MAH stating all grounds for rejection.	**EMEA/CPMP/EU Commission** • For making the final decision in the variation procedure Article 10 as laid down in Regulation 2309/93/EEC [11] applies (see also 1.2.4). The final decision shall take effect retroactively to the day of the opinion notified by the EMEA.

2.2 Type II variation

2.2.1 Time scales



2.2.2 Actions to be taken by applicant, EMEA/CPMP

NOTE:
The right column of the following chart is focussing all relevant and binding actions for Type I procedures described in regulation 542/95/EC. These have been described in more detail in the guideline of the NtA. Only the additional recommendations given by the NtA to the regulation are shown in the left column.

Steps Centralised Type II	Notice to Applicants (Volume IIA, Chapter 5/7) [13]	Regulation 542/95/EC [10]
(1) Application	**Applicant** • As for the MRP the applicant has to ensure that the criteria for a new application are not fulfilled, i.e. the variation is classified as a type II variation according to the <guideline on the categorisation of new applications (NA) versus variation applications> [3]. • It is recommended that changes on SmPC/label or insert are highlighted. • The EU Application form should be used. • The intention to apply for a variation has to be communicated to the EMEA. At least one month prior the intended date for submission the strategy and a Rapporteur is determined. If appropriate a Co-Rapporteur is nominated as well. • The MAH should ensure that the correct languages and number of copies are provided, see also Chapter VII of Volume 2A of NtA. • Submission should be done simultaneously to EMEA and Co-/Rapporteur one week prior to the CPMP meeting. • CPMP members who wish a copy of the application should be provided with a copy of the documentation. • Sample requirements see NtA, Vol2, Chapter 7 (samples are generally not required at time of submission, however, for testing during procedure they may be requested). **EMEA/CPMP** • Once the applicant has informed the EMEA Secretariat about the intention to apply for a Type I variation a project manager is appointed. • Rapporteur and, if necessary, Co-Rapporteur are nominated. In general both remain the same as those for the evaluation of the application of the marketing authorisation in the centralised procedure. In case of transfer of a MA a new Co-/Rapporteur new may be appointed. • Timelines and strategy will be defined. • After submission the EMEA Secretariat will validate the application within 5 working days to start the procedure in time with the CPMP meeting.	**Applicant** • As laid down in the regulation 542/95/EC all data supporting the variation application have to be provided. All relevant documents have to be amended with reference to those to be substituted. Additionally, the corresponding expert report have to revised and presented as an addendum or update. • The relevant fee as laid down in Regulation 297/95/EC [9] has to be provided.

Steps Centralised Type II	Notice to Applicants (Volume IIA, Chapter 5/7) [13]	Regulation 542/95/EC [10]
(2) Start	**Applicant** • The applicant is informed about the start of the procedure. **EMEA/CPMP** • Once validated the clock starts. Applicant, Co-/Rapporteur and other CPMP members will be informed accordingly.	
(3) Favourable	**Applicant** • Revised mock-ups should be provided by day 20 after adopted CPMP opinion. • Once the variation is approved final revised label and leaflet have to be sent to the EMEA within a certain timeframe agreed between MAH and EMEA. **EMEA/CPMP** • At around day 60 the opinion is adopted at a plenary CPMP meeting. • The following documents have to be sent to the Commission for amendment of the existing Marketing Authorisation: draft of the proposed SmPC, manufacturing conditions and or importing conditions and conditions of the MA, draft labelling and package leaflet presented in accordance with Directive 92/27/EEC [1]. The variation assessment report has to be presented as well.	**Applicant** • Within 60 days the applicant is informed by the Agency. **EMEA/CPMP** • Within 60 days following the receipt of a valid application the Agency shall inform the European Commission and the Applicant about the positive opinion issued by the CPMP. **EU Commission** • Within 30 days after having received the favourable opinion by the EMEA the EU Commission shall release its final decision as laid down in Article 10 of Regulation 2309/93/EEC {11]. The Community register will be updated as necessary (Article 12, 2309/93/EEC [11]).
(4) Non favourable	**EU Commission** • The draft decision by the EU Commission may be different compared to the positive opinion from the Agency. This is communicated to the EMEA and the MAH stating all grounds for rejection.	**EMEA/CPMP** • The Agency has to inform the applicant in case it is of the opinion that the application made by the applicant may not be accepted. The Agency has to notify the MAH about the objections. • The Commission is informed accordingly. **EU Commission** • For making the final decision in the variation procedure Article 10 as laid down in Regulation 2309/93/EEC [11] applies (see also 1.2.4). The final decision shall take effect retroactively to the day of the opinion notified by the EMEA.

Steps Centralised Type II	Notice to Applicants (Volume IIA, Chapter 5/7) [13]	Regulation 542/95/EC [10]
(5) Amendment	**Applicant** • Within 60 days or longer the applicant may submit once amended documents highlighting all changes which had been done. • All supplementary information in the correct amount of copies are sent to the EMEA, Co-/Rapporteur and CPMP members. • If no amended data are submitted the variation application is rejected in all EU member states and a new application has to be applied for. This is not explicitly mentioned in the corresponding variation Regulation. **EMEA/CPMP** • The period of 60 days to respond to CPMP objections may be extended by the Committee or in agreement with request by the MAH.	
(6) New start	*see (2)*	*see (2)*
(7) Favourable	*see (3)*	*see (3)*
(8) Non favourable – Appeal (See also paragraph 3.3.2)		**Applicant** • Within 15 days after he has been informed by the Agency about the negative opinion the MAH may appeal. Article 9 of Regulation 2309/93/EEC [11] applies. • The MAH is informed about the final decision. **EMEA/CPMP/EU Commission** • Where the CPMP is still of the opinion that the criteria to fulfil the variation application are not met the applicant may provide written notice to the Agency that he wishes to appeal within 15 days. • The final decision is adopted with the provisions as set out in Article 10 of regulation 2309/93/EEC [11].

2.2.3 Appeal procedure

The Appeal procedure in the centralised procedure and MRP are identical.
After the MAH has been notified about the opinion by the CPMP and in accordance with Article 9 of Regulation 2309/93/EEC [11] he may appeal within 15 days. Within the following 60 days the MAH has to provide the CPMP with all grounds justifying his action.
Within 60 days the Rapporteur finalises the assessment report to the grounds for appeal which will then be provided to the EU Commission for making the decision.
The legally binding decision is made by the Commission and, if necessary, by the Council (see also Chapter 1.2.4).

2.2.4 Urgent Safety Restriction

In case of an urgent safety restriction the MAH has to react similar to the Mutual Recognition Procedure (see also section 1.2.5).
The MAH has to inform immediately the EMEA, Rapporteur, the Co-Rapporteur and MS of the provisional restriction introduced.
If no objection has been raised by the EMEA within 24 hours the notified restrictions have to be implemented and the corresponding application for this variation has to be submitted without delay. The application is handled according to the approval procedure for Type II variations as laid down in Commission Regulation 542/95/EC [10].
The VAR will focus primarily on Pharmacovigilance issues. The critical risk benefit re-evaluation is based on all relevant data and studies of that medicinal product.
Restrictions in indication, dosage and/or target species as well as adding of contraindications, warnings and/or extending a withdrawal period are considered for a revision of the product information.

F Submission requirements

Applications to a MA contain administrative information and further documentation to proof quality, safety and efficacy of the medicinal product.
Changes to an existing marketing authorisation have to be identified and follow the procedures as foreseen in the respective regulations. The MAH is requested to apply for a variation.
For each variation application the relevant dossier requirements have to be taken into account (in NtA or CTD format, as applicable).
Based of the type of variation and the procedure (national or community) fees have to be paid, accordingly.
All relevant documents have to be submitted.

1 Regulatory background

With the implementation of any variation to a MA the achieved harmonisation should be maintained.
The Commission regulations 541/95/EC [8] and 542/95/EC [10], as amended, set out common variation procedures in MRP and centralised procedures. This fact is supported by the common approach of the application form for Type I and Type II variations, in both the MRP and centralised procedure. The documentation and supporting data to demonstrate compliance with the conditions to be fulfilled are pointed out in the two regulations mentioned above.

Procedural and documental guidance is given mainly by supporting guidelines as follows:

- Guideline on dossier requirements for type I variations [4]
- Notice to Applicants [13]
- Guideline on the categorisation of new applications (NA) versus variation applications [3]

In addition, it is useful to follow the recommendations of the MRFG. Although unofficial its advice is useful to facilitate the variations in Mutual recognition procedures.
Both, industry and health authorities may benefit to successfully implement changes and to ensure the safety of the product.

2 Application form

With each application to a marketing authorisation the <Application form for a variation to a marketing authorisation>(see Appendix 1) has to be submitted. Further details may be found in the NtA, Vol. 2A [13].
This form contains all relevant information about the variation. It is applicable for human and veterinary medicinal products, for a community (centralised procedure) or national (mutual recognition) procedure, and Type I or Type II variation. For MRP applications the RMS and all CMS have to be indicated. Abbreviations to the European countries can be found in the NtA, Vol. 2, Chapter 5 [13].
For a MRP the variation number has to be stated to allow and to assure clear identification of each variation procedure by the following scheme:
- - / - / - - - - / - - / - - - / - - (for instance DE / H / (0)118 / (0)3 / V(0)1 / R(0)1)
This code indicates a Type I or Type II variation (V for Type I and W for Type II). Further details may be found in the NtA, Vol. 2, Chapter 2 [13].
The application form may be used for authorities' comments to be made on the variation application (for instance if an application is refused). Furthermore, information about the applicant, the MAH, the product and the reason of a change has to be given. The respective type I or type II variation (to tick in a box) and the volumes concerned of the dossier have to be listed. More than one change may be included on one application form. However, this is applicable only for consequential changes. The main change has to be highlighted on the second page of the application form. Cross reference to related applications should be stated avoiding conflicts with still pending procedures.
Justifications for a general proposed change, consequential or related changes have to be given in the background section on the third page of the application form.
Present and proposed (clearly highlighted) wording of a change shall be listed. If applicable, separate documents (SmPC, label, leaflet) have to be provided. Labelling and package leaflet have to be in accordance with the Directive 2001/83/EC [1].
Finally the application form has to be signed and dated.

3 Dossier requirements

For a type I variation the respective fees have to be paid and the application form including all supporting data (see also <Guideline on dossier requirements for type I variations> [4]) have to be submitted.
For a type II variation the application form and all necessary documents including expert report, amended dossiers, etc. have to be submitted. The fees have to be paid, accordingly.
This is applicable for mutual recognition and centralised procedures.
The time of payment and the amount of fees varies in the MS and based on the procedure (see also 4 Fees)
The required languages to be used vary in the documents to be submitted and are country specific.

The amount of copies required differs depending on the procedure (mutual recognition or centralised), on the variation (type I or type II), the amended part and the member states concerned
When a variation leads to changes of the inner/outer label and/or package leaflet, revised mock-ups or specimens should be included in the variation application. Furthermore, additional data may be requested by several countries. Once a variation is granted in a centralised procedure a specimen has to be sent to the EMEA for check before the medicinal product is placed on the market.
In addition some countries may request samples ((non-)active substance/finished medicinal product, respectively).
For further information see also NtA, Vol. 2, chapter 7 [13].

4 Fees

The fees can be found on the respective national web pages, the EMEA and in Council Regulation 297/95/EC [9]. Also in the IDRAC database a continuous update of all relevant fees is available.
In the following the current fees for variations in national (mutual recognition) and community (centralised) procedures are listed:

- *Variation procedure (MRP)*
  The fees vary nationally in the European Union. Depending on MS the payment must accompany the application or fees have to be paid after receipt of invoice.
  To give an example the following fees in a MRP have currently to be paid in Denmark (DK) for medicinal products:

	DK as CMS	**DK as RMS**
Type I	134,39 € (83,99 € type I administrative)	211,66 €
Type II	182,78 € (for type II complex the same)	845,32 € (1.411,19 € type II complex)

  The fee for arbitration/referral triggered under Article 15 of Directive 75/319/EEC, as amended [2], in the MRP is 10.000€.

- *Variation procedure (centralised)*
  Type I 5.000 €
  Type II 60.000 € (30000 €, if detailed scientific evaluation not required)
  All fees shall be due on the date of receipt of the relevant application by the EMEA.

G Variation Assessment Report

Variation Assessment Reports (VAR) are prepared for human and veterinary medicinal products. They are key documents explaining the reason of approval or rejection in major variation procedures in Mutual Recognition Procedure or Centralised Procedures. The respective health authorities prepare them.
They focus all supporting data submitted for each variation. A critical, comprehensive but concise analysis of the variation should address quality, safety and efficacy as appropriate. Each deviation from existing guidelines should be stated to draw clear conclusions. The revised SmPC in the view of the proposed variation and SmPC by the MAH should be clearly justified and appended to the VAR. A reasoned opinion in the VAR for the protection of human and animal health should therefore be the basis for such reports [14].

H Communication form

A communication form (see also NtA, Vol. 2A, Chapter 5, section 6 [13]) (Appendix 2) may be used by the RMS and CMS to inform about relevant actions and stages of the process. Details for variations are completed by the MAH on the top of such page.
However, standard letters to communicate between MS may also been used.

I Examples

1) Case 1 - Initial Submission/Type II Variation (MRP)

Background

- Approval of a new medicinal product was granted in 7 of 10 EU countries after MRP Application
- Application was withdrawn in 3 countries during the MRP (insufficient clinical data confirming the dosing regimen of that product)
- New clinical data generated (ongoing clinical trial during the first MRP application)

Objective

- Get the approval in all 10 EU countries

Solution

- Based on the new data from the finalised clinical trial application of a Type II variation
- Update of the dossier/SmPC in those 7 countries where the product was already approved
- Release of a new Assessment Report (VAR) and a revised SmPC valid for all 7 countries
- Initiation of a second MRP in the remaining 3 countries (second wave), RMS remains the same, release of the AR and of the VAR by those three countries, identical SmPC
- Keep an interactive dialogue with the RMS and establish close communication with the national countries/health authorities to guarantee success in this strategy

Submission, preconditions for the Type II variation

- Check variation versus new MA application [3]
- Identify changes as Type II variation
- Ensure correct application, one for each change, unless consequential

Submission, data/documents for the Type II variation (see Variation Regulation 541/95/EC as amended, Article 6 [8])

- Completely filled, signed and dated application form
- Supporting data to part I and IV of the dossier
- Amended documentation to the dossier (updates to respective parts of the dossier, highlighted changes to SmPC/label/leaflet, present and proposed versions)
- Update/addendum to the expert report
- Fees

2) Case 2 – Type I variation (MRP/Centralised Procedure)

Background

- Change in the colouring system of the product (replacement of the colourant of the tablets)

Objective

- Efficient, fast processing and acceptance of that change as a Type I variation

Precondition for Type I variation (show that conditions as laid down in No. 5 of Annex I of 541/95/EC [8] or respectively 542/95/EC [10}, as amended, have been met)

- Same functional characteristics
- No change in dissolution profile of the solid dosage form
- Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the formulation

Submission, data/documents

- Completely filled, signed and dated application form
- Supporting documents (see Guideline on Dossier requirements for Type I variations [4])
- Revised SmPC, label, leaflet where applicable
- Samples of the new product to be provided, where applicable (see NtA, Vol. 2A, Chapter 7, Section 5.2 [13])
- Declaration that the appropriate stability tests will be performed in accordance with the relevant stability guideline and that at least 3 month stability data are at the disposal (at least two pilot scale or industrial scale batches); data should be provided if out of specification
- Declaration that the release and end-of-shelf-life specifications have not been changed
- Data that demonstrate no interfering between the new “excipient” and the finished product
- Amended documents to the relevant sections of approved dossier (Parts II A, II B, II C, II E; the proposed colourant must be in accordance with Directive 87/25/EEC; identification method of the new colourant should be included
- Fees

J Conclusion

The current variation regulations are very complex and allow low flexibility. The time frames are set legally and changes to a Marketing Authorisation are defined.
Nevertheless it may happen that a variation application is declared as invalid or deficient, or that the MAH withdraws an application during the procedure.

In the following the most important aspects that have to be considered by MAH and health agencies, are listed:

For Industry:

- To be aware of binding Regulations and Directives transferred in national law
- Data to be generated and submitted remain the same in MRP and centralised procedures
- Guidelines

- Fees
- Communication (internally, externally with health authorities)
- Transparency
- Anticipation at each step
- Team work and partnership with consultants or local contact persons in the respective European countries
- Missing or deficient data/documents (justification, pages incorrect or missing, proposed sections inconsistent with the documentation, no highlighted changes, missing ER, no dates and signs, incorrect licence details, incorrect number of copies)
- National special requirements for MRP procedures (different needs of documents to be submitted)
- Simultaneous variation not affecting each other directly should be avoided
- No variation application in August as less capacity of the health authorities

For Health authorities:

- Transparent working
- Regulations, Directives and Guidelines allow to focus on variations that require detailed assessment
- Facilitate procedures without scarifying legal aspects (divide between relevant and less relevant)

Consequently, it can be pointed out that the realisation of success of a variation and the optimisation of internal sources can only be achieved by strong considerations of legal requirements and the respective guidelines.

K Outlook

Experiences indicate that the current procedures for Type I and Type II variations for centralised and Mutual Recognition Procedures as set out in the Commission Regulations (EC) 541/95 [8] and 542/95 [10] as amended, are very complex and don't allow enough flexibility.
The increasing number of marketing authorisations may lead to an exceeding number of updating variations that have to be managed.

Both, the authorities and the marketing authorisation holder are confronted with the fixed tight time frames and strict requirements to changes to be implemented.

Therefore, the European Commission currently has started the initiative to improve the existing variation regulations. The amended regulations shall offer benefit to the health authorities and the industries.
By achieving a common assessment the variation procedures shall be simplified to reduce time, costs and manpower.
For variations in Mutual Recognition Procedures there exists the wish to induce mutual recognition.
Especially with respect to article 25 of Council Directive 2001/83/EEC [1] stating that an Authorisation does not affect the civil and criminal liability, the person responsible for his product is very much interested to be allowed to implement negative aspects into the SmPC and leaflet provided for the patient by applying for a minor Type I variation only.
Long discussions about timetables between health authorities should not affect a delay in the implementation of an USR.

“You are not only responsible for the things you do but also for those you do not. Do the right at the right time.”
This statement as a basis for success in a wide field includes a lot of responsibility and awareness for necessary actions to be taken to ensure efficacy, quality, reliability and safety in the medicinal area.

In view of public health efficient procedures to continuously updating a MA shall be the basis to speed up development and approval of new and innovative medicinal products without sacrificing critical quality, efficacy or safety data.

L Summary

This document is to describe variations to the terms of a Marketing Authorisation granted via national (mutual recognition) and community (centralised) procedures.

Taking into account the different needs of changes to a Marketing Authorisation (MA) the MAH has to demonstrate compliance with the regulatory conditions to be fulfilled.

Administrative and/or more substantial changes and procedures, which require an approval, are set out in the two Commission Variation Regulations (541/95/EC and 542/95/EC as amended respectively).
Two types of variations are defined and described in this document. Type I Variation (minor variation, notification procedure) and Type II Variation (major variation, approval procedure).
Changes, which fundamentally alter the MA, can not be considered as a variation. A new application has to be applied for. In Annex II of both regulations the respective changes are set out. This document does not give further details on such changes.

After an authorization has been issued in accordance with the respective regulation, based on new experiences the person responsible for placing a medicinal product on the market has to ensure and to adopt continuously quality, safety and efficacy of the product.
With respect to the methods of production and control provided for as set out in the second paragraph of Article 4 of Directive 65/65/EEC, the MAH has to consider any technical and scientific progress and shall make any amendments that may be required to enable the medicinal products to be manufactured and checked by means of generally accepted scientific methods.
As an authorization does not affect the civil and criminal liability (2001/83/EEC, Art.25) the MAH has forthwith to inform all relevant competent authorities of any safety relevant information which might entail an amendment of the respective documents, for instance the approved summary of product characteristics. Any prohibition or restriction imposed by the competent authorities of any country has to be communicated which might influence the evaluation of the benefits and risks of the medicinal product concerned. The aforementioned person has to apply for approval for these amendments in accordance with the respective Regulation.

A lot of papers and recommendations are released for easier understanding and guidance.
The procedures to the respective variations and dossier requirements are pointed out by giving reference to the respective legal requirements and guidelines.
Special requirements have to be considered for both procedures in both types of a variation.

The existing variation regulations are very complex and allow low flexibility. The time frames are set legally and changes to a Marketing Authorisation are defined.
Currently the European Commission has started the initiative to improve the existing variation regulations. The amended regulations shall offer benefit to the health authorities and the industries.
By achieving a common assessment the variation procedures shall be simplified to reduce time, costs and manpower.

Consequently and in view of public health, efficient variation procedures to continuously updating a MA shall be the basis to speed up development and approval of new and innovative medicinal products without sacrificing critical quality, efficacy or safety data.

M. References

[1] Directive 65/65/EEC and 92/27/EEC amended by 2001/83/EC

[2] Directive 75/319/EEC amended by 2001/83/EC

[3] Guideline on the categorisation of new applications (NA) versus variation applications, Brussels, January 2002

[4] Guideline on Dossier requirements for Type I variations, November 1999

[5] Best Practice Guide on Break-out sessions, March 26th, 2001

[6] MRFG Best Practice Guide for the handling of Variations in the Mutual Recognition Procedure: Type II Variations, 13 December 1999

[7] MRFG Procedure for Validation of Mutual Recognition Procedures for Variations, 12 November 2001

[8] Commission Regulation 541/95/EC, amended by Commission Regulation (EC) 1146/98 of 2 June 1998

[9] Council Regulation 297/95/EC, amended by Commission Regulation (EC) 2743/98, December 1998

[10] Commission Regulation 542/95/EC, amended by Commission Regulation (EC) 1069/98 of 26 May 1998

[11] Council Regulation (EEC) 2309/93, amended by Commission Regulation (EC) 649/98 of 23 March 1998

[12] MRFG SOP, Urgent Safety Restriction Member State SOP, 26 March 2001

[13] Notice to Applicants, Volume 2A, 1998 Edition

[14] Variation Assessment Report (VAR) for Veterinary Medicinal Products in the centralised and MR procedures (EMEA/CVMP/014/97)

[15] Note for guidance on Rapid Alert System (RAS) and Non-Urgent Information System (NUIS) in human Pharmacovigilance (CPMP/PhVWP/005/96/Rev.1)

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Appendix 1

APPLICATION FOR VARIATION TO A MARKETING AUTHORISATION

HUMAN ☐ **VETERINARY** ☐

COMMUNITY AUTHORISATION ☐ **NATIONAL AUTHORISATION** ☐

FOR NATIONAL MAS: IS THE PRODUCT WITHIN MUTUAL RECOGNITION? Yes ☐ No ☐

If YES, state the route used: MUTUAL RECOGNITION PROCEDURE ☐

REFERRAL [Articles 11, 12 (DIR 75/319/EEC) or Articles 19, 20 (DIR 81/851/EEC)] ☐

EX-CONCERTATION PRODUCT ☐

and state MR procedure variation number: _____

Reference Member State _____ **Concerned Member States** _____

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

Type II ☐ **Annual variation for human influenza vaccines (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: _____

Applicant's 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 Authorisation

☐ The Competent Authority refuses your request to vary the Marketing Authorisation *(reasons below)*

Signed _____ Date _____

Member State/Agency _____ Contact _____

NOTIFICATION WITH GROUNDS (TYPE I)/SUPPLEMENTARY INFORMATION (TYPE II)/REASONS FOR REFUSAL

Appendix 1

TYPE I CHANGES *(Tick against the appropriate change required)*

Supporting data: Volume(s _____ pages_____

1	Change following modification(s) to the manufacturing authorisation(s) - change in name of manufacturer or actual site of manufacture (change/withdrawal).	☐	**17**	Change in specification of the medicinal product	☐
2	Change in the name of the medicinal product (either invented name or common name)	☐	**18**	Synthesis *or* recovery of non-pharmacopoeial excipients which had been described in the original dossier.	☐
3	Change in the name and/or address of the marketing authorisation holder	☐	**19**	Change in specification of excipients *in the medicinal product* (excluding adjuvants for vaccines)	☐
4	Replacement of an excipient with a *comparable* excipient (excluding adjuvants for vaccines and biologically derived excipients)	☐	**20**	Extension of shelf-life *as* foreseen at time of authorisation	☐
5	Change in the colouring system of the product (addition, deletion or replacement of colourant(s))	☐	**20a**	Extension of the shelf-life or retest period of the active substance	☐
6	Change in the flavouring system of the product (addition, deletion or replacement of flavour(s))	☐	**21**	Change in shelf-life after first opening	☐
7	Change in coating weight of tablets or change in weight of capsule shells	☐	**22**	Change in shelf-life after reconstitution	☐
8	Change in the qualitative composition of immediate packaging material	☐	**23**	Change in the storage conditions	☐
9	Deletion of an indication	☐	**24**	Change in test procedure of active substance (✱only if the test procedure is not a physico-chemical method)	☐
10	Deletion of a route of administration	☐	**24a**	Change in test procedure for a starting material or intermediate used in manufacture of the active substance	☐
10a	Addition or replacement of measuring device for oral liquid dosage forms and other dosage forms	☐	**25**	Change in test procedures of the medicinal product (✱only if the test procedure is not a physico-chemical method)	☐
11.	Change in the manufacturer(s) of active substance✱	☐	**26**	Changes to comply with supplements to pharmacopoeias[1]	☐
11a	Change in the name of a manufacturer of the active substance	☐	**27**	Change in test procedures of non-pharmacopoeial excipients	☐
11b	Change in supplier of an intermediate compound used in the manufacture of the active substance	☐	**28**	Change in test procedure of immediate packaging	☐
12.	Minor change of manufacturing process of the active substance✱	☐	**29**	Change in test procedure of administration device	☐
12a	Change in specification of starting material or intermediate used in the manufacture of the active substance	☐	**30**	Change in pack size for a medicinal product	☐
13	Batch size of active substance✱	☐	**31**	Change in container shape	☐
14	Change in specifications of active substance□	☐	**32**	Change of imprints, bossing, or other markings (except scoring) on tablets or printing on capsules, including addition or change of inks used for product marking	☐
15	Minor changes in manufacture of the medicinal product✱	☐	**33**	Change of dimensions of tablets, capsules, suppositories or pessaries without change of quantitative composition and mean mass	☐
15a	Change in in-process controls applied during the manufacture of the product	☐	**34**	Change in the manufacturing process of a non- proteinaceous component due to the subsequent introduction of a biotechnology step	☐
16	Change in the batch size of finished product✱	☐			

TYPE II CHANGES (*Tick against the appropriate change required and detail the supporting data)*

A.	Change to Part I dossier	☐	Volume(s) _____ pages _____	Expert Report
B.	Change to Part II dossier	☐	Volume(s) _____ pages _____	Updated ☐
C.	Change to Part III dossier	☐	Volume(s) _____ pages _____	Addendum ☐
D.	Change to Part IV dossier	☐	Volume(s) _____ pages _____	

State nature of change:

Type I changes for which Type II procedure applies - if a specific manufacturing site inspection is required ☐ or ✱ applies to products covered by the following: *(Tick the relevant box)*

Immunological 89/342/EEC (✱) ☐
Blood Product 89/381/EEC (✱) ☐
Veterinary Immunological 90/677/EEC (✱) ☐
High Technology 87/22/EEC (List A) (✱) ☐
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 34/ A to D)*

[1] In cases where the marketing authorisation holder refers to the current edition of the pharmacopoeia, no variation application is required provided the change is introduced within six months of adoption of the revised monograph.

Appendix 1

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.)

PRESENT	PROPOSED

I hereby make application for the above Marketing Authorisation 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_____

Appendix

FOR MUTAL 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 tot he 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, referrd to Agency on _____ *(date)*

CONDITIONS FOR ACCEPTANCE / REASONS FOR NON-ACCEPTANCE

Signed _____ Date _____