Impact of the new Variation Regulations 1084/2003 and 1085/2003 on the industrial practice of a multinationally operating pharmaceutical company with regard to the EU enlargement and the multinational procedure in performing variations

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1 List of Abbreviations

AMPAC	Analytical Methods Post Approval Changes
ANDA	Abridged New Drug Application
API	Active Pharmaceutical Ingredient
AR	Annual Report
ATC	Anatomical therapeutic chemical
BACPAC	Bulk Actives Postapproval Changes
CADREAC	Collaboration Agreement between Drug Regulatory Agencies in EU Associated Countries
CBE	Change Being Effected
CDER	Center of Drug Evaluation and Research
CEP	Certification of European Pharmacopoeia
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CMC	Chemistry, manufacturing and control
CMS	Concerned Member State(s)
CoA	Certificate of Analysis
CP	Centralised Procedure
CPMP	Committee of Proprietary Medicinal Products
CR	Commission Regulation
CTD	Common Technical Document
CTM	Community Trademarks
EC	European Community
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EEC	European Economic Community
EFPIA	European Federation of Pharmaceutical Industries and Associations
e.g.	for example
EMEA	European Medicinal Agency
EU	European Union
FD&C	Food Drug and Cosmetic
FDA	Food and Drug Administration

FVAR	Final Variation Assessment Report
GMP	Good Manufacturing Practice
i.e.	that is
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MHLW	Ministry of Health Labour and Welfare
MR	Mutual Recognition
MRA	Mutual Recognition Agreement
MRFG	Mutual Recognition Facilitation Group
MRP	Mutual Recognition Procedure
MS	Member State(s)
NCE	New Chemical Entity
NIR	Near Infrared Spectroscopy
NDA	New Drug Application
No.	Number
NtA	Notice to Applicants
PAL	Pharmaceutical Affaires Law
PAS	Prior Approval Supplement
Ph. Eur.	European Pharmacopeia
PVWP	Pharmacovigilance Working Party
QWP	Quality Working Party
resp.	respectively
RMS	Reference Member State
SmPC	Summary of Product Characteristics
SUPAC-IR	Scale-up and post approval changes: Immediate release solid oral dosage forms
SUPAC-MR	Scale-up and post approval changes: Modified release solid oral dosage forms
SUPAC-SS	Scale-up and post approval changes: Nonsterile semisolid dosage forms
SUPAC-TDS	Scale-up and post approval changes: Transdermal delivery systems
TSE	Transmissible spongiforme encephalopathy
UK	United Kingdom
US	United States
USA	United States of America
USR	Urgent Safety Restrictions

2 Introduction

During their life cycle, medicinal products are generally subject to a multitude of changes. The driving forces for these changes are manifold, e.g., the need to introduce process and production improvements, market demands, the continuously evolving requirements of regulatory bodies, as well as the experience gained with the product over time. Indeed, pharmaceutical companies are obliged to review regularly the manufacturing methods and test procedures in the light of scientific and technical progress.

The marketing authorisation holder (MAH) is responsible for ensuring compliance between the approved documentation of the marketing authorisation and the actual, current status of the medicinal product in practice. That means that the competent authority has to be informed of every change to a marketing authorisation, which has an impact on the documentation and therefore probably affects the assessment of the medicinal product regarding its quality, safety and/or efficacy.

Variations account for a very high proportion of the workload of authorities and MAHs. On an average three, to four variations are submitted per product and year within the EU variation procedures, which means that up to 80 % of the regulatory workload is devoted to the maintenance of existing products (EFPIA Regulation 2000 [1]). What is more, the number of minor variations is increasing. A constantly increasing number of mutual recognition (MR) applications, that are expected after the accession of ten new Member States (MS) to the European Union (EU) on 1 May 2004, will also lead to an increasing number of variations and more MS will participate in a variation procedure.

The experience of the past has shown that a revision of the Variation Regulations was necessary to provide a simplified procedure for managing variations, to reduce the workload for both competent authorities and industry, and to build a variation system suitable for the EU enlargement. This revision should involve the definition and classification of different types of changes, the deletion of inconsistencies and repetitions in Annex I of the Variation Regulations and the determination of the corresponding documentation to support the change in order to provide a more structured variation system as compared to the former one.

The final version of the revised EU-Variation Regulation, the *Commission Regulation (EC) No. 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State* [2] and the *Commission Regulation (EC) No. 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No. 2309/93* [3], entered into force on 17 July 2003 and applied from 1 October 2003. These Commission Regu-

lations replace the Commission Regulation (EC) No. 541/95 of 10 March 1995 [4] and Commission Regulation 542/95 of 10 March 1995 [5].

Multinationally operating companies do not only hold marketing authorisations in the EU, but also in non-European markets. Despite the progress on regulatory guidance for post-approval changes, the regulatory requirements are still not globally harmonised. Global pharmaceutical companies are therefore faced with country- and region specific change reporting categories, documentation requirements, submission procedures and approval times. For this reason, industry would appreciate to reduce this regulatory burden and to simplify and adapt the variation procedures in at least the main industry regions EU, USA and Japan.

This Master-Thesis discusses the impact of the new European Variation Regulations on the industrial practice of a multinationally operating pharmaceutical company and highlights the advantages and disadvantages in performing variations according to these Regulations in the enlarged European Union and their suitability regarding the multinational procedure in performing variations.

3 Innovations of Commission Regulation 1084/2003 and 1085/2003

Commission Regulation (EC) No.1084/2003 (in the following CR 1084/2003) [2] and Commission Regulation (EC) No. 1085/2003 (in the following CR 1085/2003) [3] provide the same regulatory framework for variations of products granted by mutual recognition procedure (MRP) and centralised procedure (CP). The basic principles of classification, the procedures and the time lines are identical. However, for variations according to CR 1084/2003 [2] the competent authorities of the Reference Member State (RMS) and Concerned Member States (CMS) are involved in the procedures, whereas for variations according to CR 1085/2003 [3] only one authority, the European Medicinal Agency (EMEA), is involved.

According to these Regulations a differentiation between minor variations of type IA and type IB, major variations of type II and extensions is made.

It is stated explicitly in the Regulations, that where a variation of type IA, IB or II requires consequential revision of the SmPC, labelling and package leaflet/insert, this is considered as part of the variation (Article 4(4), 5(4), 6(4) of CR 1084/2003 [2] and 1085/2003 [3]).

3.1 Notifications – Introduction of a new Annex I

The changes fulfilling the conditions listed in Annex I of CR 1084/2003 [2] and 1085/2003 [3] are considered to be minor variations (Article 3 paragraph 2 of CR 1084/2003 [2] and 1085/2003 [3]), also called notifications. These changes comprise administrative changes and changes to the chemistry, manufacturing and control section (Module 3) of the dossier.

There are two subtypes of notifications: Notifications type IA and notifications type IB. In the previous Variation Regulations only one type of minor variation was classified.

The revised Regulations provide therefore a new Annex I, specifying now 46 minor changes (47 minor changes according to CR 1085/2003 [3]), that is to consult for changes of a type IA and IB notification.

Compared to the former Regulations, which listed 33 changes, Annex I has been restructured and the following changes have been newly introduced to Annex I: Change in ATC-Code (No. 6), submission of a new or updated TSE CEP for an active substance or starting material, reagent, intermediate (No. 16), submission of a new or updated CEP or TSE CEP for an excipient (No. 21, 22), change in source of excipient or reagent from a TSE risk to a vegetable or synthetic material (No. 23), change in supplier of packaging components or devices (when mentioned in the dossier) (No. 30) and change in the SmPC of an essentially similar product following a Commission Decision for a referral for an original medicinal product (No. 46).

The *Guideline on Dossier Requirements for Type IA and IB Notifications* [6] states which documentation should be submitted with these notifications.

3.1.1 Notifications of type IA

The changes listed in Annex I of the Regulations 1084/2003 [2] and 1085/2003 [3] that do not affect the granted quality, safety and efficacy of the medicinal product are categorised as notifications of type IA. These changes can therefore be implemented without an evaluation.

This classification and the corresponding procedure are newly introduced to the variation system. For medicinal products authorised by MRP, the RMS exclusively coordinates notifications of type IA and the submitted documentation is checked for validity by the RMS on behalf of all CMS within 14 days. (Article 4 (5) of CR 1084/2003 [2]). The RMS undertakes a check, which is more extensive than an administrative check, to come to a decision on validity of the notification based on the submitted documentation (MRFG *Best Practice Guide for the Processing of Type IA Minor Variations (Notifications) in the MRP* [7]). The RMS informs the MAH in writing and all CMS whether the notification is valid or invalid.

For centrally authorised medicinal products, the EMEA follows an analogous procedure (Article 4 of CR 1085/2003 [3]). The Rapporteur receives a copy of the type IA notification for information. However, validity check is only done by the EMEA. (*EMEA Post-Authorisation Guidance Human Medicinal Products* [8]). For notifications of type IA, the Commission shall, where necessary, and based on a proposal prepared by the EMEA update every 6 months the marketing authorisation (Article 4 (5) of 1085/2003 [3]). The innovation is that the Commission is allowed to group the updates of the marketing authorisation every six months in one single decision to simplify the procedure.

Due to the above-described procedure, changes of type IA are also called "tell and do" changes.

3.1.2 Notifications of type IB

The changes listed in Annex I of the Regulations 1084/2003 [2] and 1085/2003 [3] which necessitate demonstrating that the granted quality, safety and efficacy of the medicinal product are not affected, are classified as notifications of type IB. Type IB notifications follow more or less the former procedure for type I variations.

Like the previous Regulation for MR variations, the new Regulation provides an implicit approval: The notification shall be deemed to have been accepted within 30 days (Article 5 (6) of CR 1084/2003 [2]). In cases where the notification cannot be accepted, the MAH shall be informed by the RMS within 30 days (so called "Notification With Grounds"). Upon receipt of a "Notification With Grounds", the MAH has 30 days in order to submit an amend-

ment to the notification. The procedure will then be restarted. (Article 5 (8) of CR 1084/2003 and *MRFG Best Practice Guide for the Processing of Type IB Minor Variations (Notifications) in the MRP* [9]).

However, there is one major innovation for MR variations. The RMS on behalf of all CMS does the coordination and evaluation of the change. Only in exceptional cases may the RMS seek an opinion from the CMS. This holds true for a change in the name of the medicinal product (change no. 2 of Annex I) or change in pack size (change no. 41a2 and 41b of Annex I). Due to the reason that a MS is not legally authorised to make decisions for another MS, it is newly introduced that the CMS now have the right to arbitration. The right to arbitration applies as well to the MAH (Article 5 (11) of CR 1084/2003 [2]).

For centrally authorised products, there is an analogous procedure for type IB notifications (Article 5 of CR 1085/2003 [3]). The Rapporteur is involved in the evaluation of the change (*EMEA Post-Authorisation Guidance Human Medicinal Products* [8]). It applies as well to type IB notifications that the Commission shall, where necessary and based on a proposal prepared by the EMEA, update every 6 months the marketing authorisation (Article 5(7) of 1085/2003 [3]).

The fact remains unchanged that in contrast to the CR 1084/2003 [2] for type IB notifications, the MAH has not the possibility to appeal in case of an unfavourable decision.

Due to the above-described procedure, changes of type IB are also called "tell, wait and do" changes.

3.2 Variations - Approval Procedure

The changes that are not listed in Annex I or Annex II of CR 1084/2003 [2] and CR 1085/2003 [3] are categorised as major variations of type II (Article 3 (2) of CR 1084/2003 [2] and 1085/2003 [3]).

A type II variation is a variation, which elicits a change of the quality, safety and/or efficacy of a medicinal product and necessitates an assessment. Variations of type II follow an approval procedure. As was already laid down in the previous Regulation, the RMS shall evaluate the application within 60 days and shall prepare an assessment report and a draft decision to be addressed to the CMS. Within 30 days following receipt of these documents the CMS shall recognise the draft decision. The RMS will close the procedure.

In contrast to the former Regulation, the period for preparing the assessment report and the draft decision may be reduced with regard to the urgency of the matter particularly for safety issues. Besides, changes to or addition of a therapeutic indication are no longer considered as new applications, but are now classified as type II variations. In cases where an extensive assessment of data is required, an extension to 90 days for preparing the assessment report and

the draft decision is possible. For variations concerning a change to or addition of a non-food producing target species, also classified as type II variations, the period to prepare an assessment report and the draft decision shall be extended to 90 days (Article 6 (7) of CR 1084/2003 [2]).

In cases in which the RMS requests supplementary information to complete the assessment, the procedure shall be suspended until the MAH has answered within the time limit set by the RMS. (Article 6 (8) of CR 1084/2003 [2]). The revised Regulation no longer fixes the concrete time limit for the clock-off period.

Decisions concerning variations related to safety issues shall be implemented in a time frame as agreed between the RMS and the MAH in consultation with the CMS (Article 6 (11) of CR 1084/2003 [2]).

It has been newly introduced to the Regulation that the MAH now has the right to arbitration, just like the CMS.

(Article 6 (13) of CR 1084/2003 [2]).

Flow charts of the procedure can be found in the Appendix I

For centrally authorised medicinal products, the EMEA follows an analogous procedure (Article 6 of CR 1085/2003 [3]). As a rule, only the Rapporteur is involved in the assessment. However, for new indications the involvement of the Co-Rapporteur is necessary and for other major variations the involvement of the Co-Rapporteur is decided by the Committee for Medicinal Products for Human Use (CHMP) on a case-by-case basis. (*EMEA Post-Authorisation Guidance Human Medicinal Products* [8]).

Due to the above-described procedure, changes of type II are also called "tell and wait" changes.

3.3 Extensions: changes to an existing marketing authorisation-revised Annex II

The changes listed in Annex II of Regulation 1084/2003 [2] and 1085/2003 [3] are categorised as extensions (Article 2 and Annex II of Regulation 1084/2003 [2] and 1085/2003 [3]). These are

— change to the active substance

— change to strength, pharmaceutical form and route of administration

— change or addition of food-producing target species.

Extensions have to be submitted as new applications, which shall be examined using the 210 days evaluation procedure referred to in Article 17 of Directive 2001/83 [10]. They do not fall under the scope of CR 1084/2003 [2] and 1085/2003 [3]).

The most important innovation of the revised Annex II is the deletion of changes to therapeutic indications, which are now filed as type II variations.

3.4 Urgent safety restrictions

The revised Regulations contain procedural changes for urgent safety restrictions (USR): The MAH is still required to inform the competent authorities/the EMEA immediately about taking USRs. The USR is accepted if no objection is raised within 24 hours by the competent authorities/the EMEA. The USR shall be implemented within a time frame to be agreed with the competent authorities/the EMEA. In comparison with the previous Regulations, it is no longer required to meet the 24-hour deadline for implementation. On the other hand the time frame for submitting the corresponding variation is now determined. The variation application (Type II) reflecting the USR should be submitted within 15 days after the initiation of the USR. In the event that competent authority(ies) impose an USR on the holder, the holder is obliged to submit a corresponding type II variation. [11]

4 Discussion of impact of the Commission Regulation 1084/2003 on the industrial practice in performing variations with regard to the EU enlargement

After the accession of ten new MS on 1 May 2004, national MAs in the new MS can be maintained as long as they comply with EU requirements. But the Commission advises a harmonisation of these products with the MRP outcome. Although the inclusion of the new MS in a MRP is voluntary, the repeat-use procedure is recommended. For MA, registered through the CADREAC procedure, a 30-day repeat use MRP will apply. Therefore, a high number of additional MRP waves are expected to take place after the accession to include the new MS [12]. Consequently, this has a profound impact on industry in managing MRP variations, as more MS will participate in the variation procedure. Due to this fact, both industry and authorities asked for a streamlined and practical variation system in order to cope with the increased workload and to facilitate the implementation of changes in the enlarged EU.

This chapter discusses the impact of CR 1084/2003 [2] on realization of a simplified variation system from industry's point of view.

4.1 Classification of variations and the supporting documents for filing variations

4.1.1 Minor variations of type IA and IB

A general approach of the revised Annex I and the corresponding *Guideline on Dossier Requirements for Type IA and IB Notifications* [6] is to reduce the amount of supporting documentation that is to be provided by the applicant to the authorities, but at the same time safeguard that minor variations lead to a medicinal product of the same quality, safety and efficacy.

According to this approach, the variation application for minor variations should contain a checklist (copied from the above-mentioned guideline [6]) asking the applicant to confirm (cross-out each item) that all the required conditions are satisfied and the required documentation is submitted. Besides, a box to cross out declarations of the applicant for type IA and IB variations has been included in the application form, so that written declarations are not necessary anymore. Instead of providing a declaration that stability studies have been started and at least 3 months data are available according to the previous *Guideline on Dossier Requirements for Type I Variation* [13], this requirement is stated as a condition and the batch numbers of the batches used in stability studies should be indicated in the documentation (e.g. change no. 34 [6], change no. 5 [13]).

This practice allows performing a notification procedure, which facilitates the work of the competent regulatory authorities to cope with an increased number of minor variations in the enlarged EU. At the same time, concrete information is provided on batches used to generate the data to support the change that will be checked by the supervisory authority during the inspection.

4.1.1.1 Administrative changes

Table 1 of Appendix 2 lists the administrative changes of Annex I and gives an overview of the impact on industrial practice. In the following, administrative changes of high significance are discussed:

With the EU enlargement, it is expected that companies as well as manufacturers of active substances and finished products will be sold to multinationally operating companies in order to extend their facilities to the Eastern European Area by now having the benefits of a single market. A change in name of the companies might occur more frequently in the future.

A change in the name and/or address of the MAH (change no. 1) is classified as a "tell and do"-change (type IA) under the condition that the MAH remains the *same legal entity*. Compared to the former Variation Regulation, the change can be implemented within a shorter time frame, which clearly is an advantage from industry's point of view. [2]

A new, increased requirement for the change in the name and/or address of the MAH is, that a formal document from the relevant official body (e.g. Chamber of Commerce) is required as a supporting document in which the new name and address is stated [6]. According to the previous *Guideline on Dossier Requirements for Type I Variation* [13], a written declaration from the companies stating that the MAH is the same legal entity was considered sufficient.

The transfer of the MA to a new holder (*different legal entity*) is still excluded from the scope of the Variation Regulation (Article 2 of CR 1084/2003 [2]) and has to be managed by national law of the MS. To transfer MAs granted through the MRP to a new holder, different time lines for each MS and country-specific requirements have to be considered. In the enlarged EU, it is expected that additional MS will be included in a MRP by repeat-use procedure and the companies have to cope with additional requirements and prolonged time lines for a transfer of the MA to a new holder. This will increase the administrative and regulatory burden to the company and represents a disadvantage with regard to the EU enlargement.

The reason for managing the transfer of a MA by national procedure is, that in the different MS of the EU different ministries are involved in a transfer of the MA of a medicinal product and the status of a registration is handled differently, e.g. a new registration licence has to be

issued by a formal procedure which would take more time and cannot be covered under the variation system for the time being.

Nevertheless, from industry's point of view the harmonisation of this issue within the EU and having the transfer of MAs granted through the MRP to a new holder included in one procedure for all concerned countries would be appreciated. The variation system could be suitable for it.

The change in name and address of a manufacturer of the finished product (change no. 5) and the change in the name and/or address of a manufacturer of the active substance, where no Ph. Eur. CEP is available (change no. 4) are now classified as type IA notifications. The reduction of the time line for implementation is highly appreciated by industry [2]. As for the change in name and/or address of the MAH, a formal document from an official body mentioning the name and address of the manufacturer has now to be provided as supporting documentation for these variations [6].

4.1.1.2 Changes in the manufacturing of the medicinal product

Table 2 of Appendix 2 lists the changes in the manufacturing of the active substance and the medicinal product, which can be considered as type IA and IB variations according to Annex I [2] and provides an overview of the impact on the industrial practice.

In the following, manufacturing changes of the finished medicinal products of high significance with regard to the EU enlargement are discussed.

4.1.1.2.1 Manufacturing transfers

With an enlarged European Union beginning from 1 May 2004, multinationally operating companies will start to reconsider their plant network strategy. Transfers of a part or all of the manufacturing process of a medicinal product to different manufacturing sites or an introduction of additional manufacturing sites will take place in order to cope with the demands of the market in the enlarged EU. It is expected that manufacturing sites of the newly acceded MS of the EU will also be included in the transfers.

Conditions and documents to be provided for site transfers can be found under change no.7: *Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product.* [2] [6]

General conditions and supporting documents for site transfers

A general condition for site transfers for any production step is, that proof has to be provided that the proposed site is appropriately authorised for the pharmaceutical form or product concerned. For this reason a copy of the current manufacturing licence and/or a GMP certifi-

cate or a statement has to be included in the documentation depending on whether the company is in the EEA, outside the EEA with or without an operational GMP mutual recognition agreement (MRA) between the country concerned and the EU. The date and scope of the last satisfactory inspection by an inspection service that took place in the last 3 years has also to be provided as a supporting document [2] [6].

For countries outside the EEA without an operational GMP MRA with the EU, companies are dependent on the relevant inspection service of one of the MS of the EEA being able to carry out the inspections at the necessary frequency [2] [6]. Even for the manufacturing sites available in the newly acceded MS of the EU, it is uncertain if these countries can cope with all GMP inspections according to EU requirements. If a proposed site is not inspected in time, there will be a delay for multinationally operating companies to transfer the product.

Industry has to take this issue into consideration, when planning site transfers.

The present and proposed finished product manufacturers have to be stated in the variation application form in order to provide an overview of the responsible manufacturers in the manufacturing process of the medicinal product concerned [6].

Replacement or addition of a site for secondary packaging

A site transfer for secondary packaging for all types of pharmaceutical forms is now classified as a type IA notification [2] and the transfer can take place in a shorter time as compared to the previous variation system. From industry's point of view, this can be regarded as an advantage, because the capacities of the machines at the new site can be used immediately after the acknowledgement of a valid notification (14 days). This enormously facilitates the planning of resources in the logistics department at least for products to be produced for the EU market.

The supporting documents for the notification are listed in the chapter *General conditions and supporting documents for site transfers.*

Replacement or addition of a site for primary packaging for a solid pharmaceutical form

The replacement or addition of a site for primary packaging for solid pharmaceutical forms is now classified as a type IA notification [2] and a quick implementation is possible. As there is no long approval period, the planning of resources can be handled flexibly and the supply chain will be improved in the EU. The supporting documents listed in the chapter *General conditions and supporting documents for site transfers* have to be provided for the notification.

Replacement or addition of a site for primary packaging for a semi-solid or liquid pharmaceutical form

Although the same supporting documents have to be provided for the replacement or addition of a primary packaging site for semi-solid or liquid pharmaceutical forms, this change is

classified as a type IB notification [2] and an evaluation of the supporting documentation is required. The reason for this is that a transfer of the filling process of a semi-solid and a liquid pharmaceutical dosage form is more critical than a transfer of the primary packaging of a solid dosage form. Nevertheless, the provided documentation, which is already pre-assessed by an inspection service, does not really justify the classification of a type IB notification but rather applies to a type IA notification. No product specific documents have to be provided in order to demonstrate that the quality, safety and efficacy of the medicinal product remain the same at the new site. The classification is questionable with regard to this point.

Replacement or addition of a site for primary packaging for liquid pharmaceutical forms (suspension, emulsion)

The change of the primary packaging site for a liquid pharmaceutical form of a suspension or emulsion is classified as a type IB notification [2]. The filling process of a ready-to-use suspension or emulsion has to be regarded as critical, because the liquid and suspended or emulsed components can easily separate. The process must therefore be consistent in order to assure uniformity of the active ingredient in the packed finished product. An evaluation of this change is justified to demonstrate that the quality of the finished product packed at the new site is the same. Validation of the filling-process at a new site reflects a state-of-the art procedure in industrial practice, which is now explicitly stated as a requirement for performing this variation in the new Variation Regulation [2].

However, the validation of the process does not necessarily have to be finished at the time of submission of the variation. A validation scheme according to Annex I of CPMP/QWP/848/96 *Note for Guidance on Process Validation* [14] can be provided as a supporting document. As a consequence, the validation and the filing of the variation can be done in parallel. By this approach, time can be saved and after approval of the variation and finishing the validation work, the validation batches can be released to market and sold in almost the assigned shelf-life. There is no long storage period for the validation batches. This approach is advantageous to industrial practice.

The validation scheme should outline the formal process validation studies to be conducted on three consecutive production scale batches. The results of these studies should be available for verification by the supervisory authority. For this purpose a report following completion of the scheme should be generated for examination by the supervisory authority containing information on validation (CPMP/QWP/848/96 [14]).

Nevertheless, companies also have the opportunity to carry out the validation prior to filing the variation [2]. In this case, the batch numbers of the validation batches (three production batches) have to be provided in the variation documentation. [6].

Except for the cases, where the results of the validation show significant deviations from those expected, the competent, regulatory authority of the RMS is not involved in the review

of the validation data in the variation procedure (CPMP/QWP/848/96 [14]). However, this does not mean that industry is relieved of the duty to carry out and document the results of the validation study accordingly.

If the above-discussed changes of a packaging site concern a sterile or a biological product, such changes have to be filed as a type II variation [2]. This restriction has not been made in the former Variation Regulation and represents a disadvantage. Companies producing sterile or biological products have to take into consideration that the variation procedure for this change will take 90 days.

Replacement or addition of a manufacturing site for all other manufacturing operations except batch release

The replacement or addition of a manufacturing site for all other manufacturing operations, except primary or secondary packaging and batch release, is classified as a type IB notification [2]. In addition to the documents of the manufacturing licence or GMP certificate/statement and the inspection date, information on validation has to be provided as described above. Batch analysis data on one production batch and 2 pilot scale batches (or 2 production batches) and comparative data on the last three batches from the previous site have to be provided. Batch data on the next 2 production batches should be available on request [6]. Therefore, companies have to plan to produce at least one production batch that can be used for validation as well, prior to filing the variation.

A transfer to a different plant for these operations cannot be filed as a minor variation for biological medicinal products. For these products, the variation has to follow a type II procedure [2].

4.1.1.2.2 Minor changes in the manufacturing process of the finished product

The transfer of a product from one manufacturing site to another is often associated with minor changes in the manufacturing process, because the new site cannot produce exactly in the same way as the previous site. Independently of a site transfer, minor changes in production represent the most frequent changes in a facility.

These changes are classified as type IB notifications [2]. They have been formerly classified as type I variations. Consequently the time frame for implementation has remained unchanged as compared to the former Regulation [4]. The conditions and supporting documentation can be found under change no. 33 of the *Guideline on Dossier Requirements for type IA and IB Notifications* [6].

From industry's point of view, the classification of a minor change in the manufacturing process of the finished product is handled too restrictively, because all minor changes are classified to follow a type IB notification. Such changes should rather be subdivided into mi-

nor changes of type IA and minor changes of type IB depending on the respective change in the manufacturing process. For example, changes in the order of solutions used in unit operations (e.g. in a granulation process) or minor changes of +/- 20 % in the mixing time, blending time or temperature should be considered as type IA notifications. This would reflect an analogous distinction to the one made by the NtA working group on changes to analytical methods. [15]

The conditions of a minor change in the manufacturing process (change no. 33) mention a new requirement: At least 3 months stability data on at least one pilot or industrial scale batch have to be at the disposal of the applicant when submitting the notification to the authorities [2]. This has to be considered when planning the change as it influences the time lines for implementation of this change in the facility.

According to the former *Guideline on Dossier Requirements for Type I Variation* [13], no stability data were required for this change.

According to the *Guideline on Stability Testing for Applications for Variations to a Marketing Authorisation* [16], the required stability studies should be generated using accelerated and long-term testing conditions. The applicant has to give the assurance that the stability studies will be finalised, i.e. up to the registered shelf-life and that the data will be provided to the competent authorities if there are outside specifications or potentially outside specifications at the end of the proposed shelf-life.

These 3 months stability data should not be submitted to authorities for review. Only the batch numbers of the batches used in the stability studies should be indicated [6]. The MAH is responsible for performing these studies in accordance with the relevant guidelines in order to support the change.

The supervisory authority will be entitled to review the respective stability data during their biannual inspection to follow-up on this notification.

It is newly introduced to the supporting documentation for this change that batch analysis data have to be provided in comparative tabulated format on a minimum of one batch manufactured to both the currently approved and proposed process. The next two full production batches should be made available upon request. [6]

The production batch used to prepare the batch analysis data can also be used to perform stability studies and as well to prepare dissolution profile data for solid oral dosage forms.

It is pointed out in the conditions that even a pilot batch can be used to perform stability studies, but in most cases it is clearly more efficient for companies to produce a full-scale batch to generate the data. This full-scale batch can be marketed after the notification procedure has been finished.

As a conclusion it can be stated, that due to the increased requirements introduced by the new Variation Regulation and the *Guideline on Dossier Requirements for Type IA and IB Notifications* [6], minor changes in the manufacturing process are more expensive than before. In order to cope with this situation, companies should make a cost-benefit analysis when planning a minor change in production. This cost-benefit analysis should take the costs for the stability studies and the production of the batch into consideration. These increased requirements have to be considered as a restriction of business flexibility.

Industry unions should suggest a more scientifically based differentiation of minor changes in the manufacturing process, as many changes appear to be suitable to be filed as type IA notifications, which do not even need an evaluation by stability data.

A clear definition of what is to be considered as a minor change in the manufacturing process would be useful. Industry's proposals for a definition of minor changes are: Not affecting a step in the manufacturing process identified to be critical to release, no change in technology and equipment, only affecting one step in the process, no change in IPC limits [15]. Based on this proposed definition a differentiation of changes suitable for type IA and type IB notification should be made. This approach would be worthwhile considering in the next revision of the Variation Regulation.

4.1.1.3 Changes affecting the quality control of the active substance and medicinal product

Table 3 of Appendix 2 lists the changes affecting the quality control of the active substance and the medicinal product according to Annex I [2] and gives an overview of the impact on industrial practice. In the following, changes of high significance are discussed.

4.1.1.3.1 Tightening of specification limits or addition of a new test parameter

Tightening of specification limits or addition of a new test parameter to the specification are changes that may be related to an active substance, a starting material, an intermediate, a reagent (change no. 12), an excipient (change no. 19), the finished product (change no. 37), or to the immediate packaging of the finished product (change no. 26). Besides, in-process tests or limits (change no. 31) can be affected. [2]

These changes are subdivided into tightening of specification limits that may be classified as type IA or IB notifications and addition of a new test parameter that is always classified as a type IB notification [2].

It should be noted that these changes are only classified as type I notifications if the change does not result from an unexpected event arising during manufacture. This condition ensures a differentiation between all permanent post-approval changes to be filed as a variation and

changes arising through unexpected events and thus documented by the deviation system of quality assurance.

Tightening of specification limits

Compared to the previous Annex I of the CR 541/95 [4], it has to be considered as an advantage that the change involving tightening of specification limits is now separated from the change addition of a new test parameter. The change tightening of specification limits is classified as a type IA notification provided that the change is not a consequence of any commitment from previous assessments to review specification limits. [2].

If the results of stability studies or a trend analysis of the batch data of a medicinal product show that the specification limit needs to be tightened, then the applicant can implement this change in a shorter time frame and with less documentation as compared to the former requirements. It is no longer required to generate comparative dissolution profiles, which has been previously requested as a supporting document for tightening of specification limits of an active substance, finished product or excipient [13].

These facts will encourage companies to adapt their specification limits to the experience of the medicinal product gained during routine production and stability studies.

If the tightening of specification limits is the consequence of a commitment from previous assessments to review specification limits (e.g. made by applicant during the procedure for the MA application or a type II variation procedure), the change is classified as a type IB variation [2]. From industry's point of view, this classification is a disadvantage, because industry fulfils commitments from an issue that has already been assessed by the authorities. An evaluation through a type IB notification with a time scale of 30 days could be considered as superfluous. Industry would rather appreciate filing this change as a type IA notification, so that commitments could be implemented after the acknowledgement of a valid notification within 14 days without further assessment.

Addition of a new test parameter to the specification

In order to add a new test parameter to the specification by a notification procedure, the following condition has to be fulfilled: The new test method does not concern a novel non-standard technique or a standard technique used in a novel way. Unfortunately, there is no definition what a non-standard technique or a novel way in using a standard technique is. For the industrial practice, this gives an uncertainty about the classification and the corresponding variation procedure for the introduction of a new test parameter to the specification.

For example, this condition excludes the introduction of the NIRS method from classification as a minor variation, as stated by the Quality Working Party [17]. The introduction of an additional NIRS test would require a type II variation. This is a disadvantage from industry's point of view, as this method is frequently used as an identification or assay test during the

production. The NIRS is an established and validated method that is described in the European Pharmacopoeia. If the requirements of the *CPMP/QWP/3309/01 Note for Guidance on the use of Near Infrared Spectroscopy by the Pharmaceutical Industry and the Data Requirements for new Submissions and Variations* [18] are fulfilled and appropriate data are provided in the variation application, this change should clearly be filed as a type IB notification to be evaluated by the RMS. A type II variation corresponding with a more extensive documentation, higher costs and a delay in implementation as compared to a type IB notification, does not seem to be justified and would prevent industry from introducing quick, convenient and reliable testing methods in production.

The addition of a new test parameter to the specification of an excipient, active substance or a starting material/intermediate/reagent requires, where appropriate, the submission of comparative dissolution data for the finished product (documentation no. 5) and a justification for not submitting a new bioequivalence study (documentation no. 6) [6]. The addition of a new test parameter usually does not result in a new or changed product. Therefore there is no necessity to prepare dissolution profiles or to justify the fact that no new bioequivalence study is submitted. These requirements are only relevant if the added test parameter relates to the physical properties of the active substance or an excipient used in solid, oral dosage forms that might have an influence on the bioavailability of the active substance.

Precise and more scientific differentiations should have been made in the requirements laid down in relation to documentation.

4.1.1.3.2 Submission of a new or updated European Pharmacopoeia Certificate of Suitability (CEP)

A new or updated European Pharmacopoeia Certificate of Suitability (CEP) for an active substance or starting material, intermediate or reagent (change no. 15) and excipient (change no. 21) is filed as a quick type IA notification, provided that all conditions are fulfilled. Exceptions are CEPs for sterile substances or substances in veterinary medicinal products for the use in animal species susceptible to TSE. These are filed as type IB notification. [2]

For notifications including a CEP and when the change concerns the dossier submitted for the application of the certificate (certification file), the documentation required for this change has to be submitted to the European Directorate for the Quality of Medicines (EDQM) [2]. This is advantageous to the manufacturers of substances complying with a monograph of the European Pharmacopoeia (Ph. Eur.), because there is one evaluation of the certification file at one site, the EDQM. The assessment of the change to the certification file by the EDQM is only based on the certification that the substance complies with the specification and is fully controlled by testing in accordance with the monograph provided in the Ph. Eur.

If the CEP is revised following the evaluation of this change, any MAs concerned have to be updated by a variation. In many cases this can be done through a type IA notification (Annex I of CR 1084/2003 [2]). If a new CEP is introduced to replace an EDMF for an active substance in the quality part of the dossier, this change can be filed as a type IA notification under the provision that the specifications and test procedures in the EDMF fully comply with Ph. Eur. and all additional (to Ph. Eur.) specifications and test procedures regarding degradation products and residual solvents mentioned in the EDMF are stated as well on the CEP. The re-test period in the CEP has to be the same as in the EDMF. If this is not the case, variations have to be filed in parallel.

The replacement of an EDMF by a CEP offers a significant advantage for the MAH. There are no EDMF-specific problems with regard to updates of an EDMF that have to be filed by a variation taking into consideration that the restricted part needs to be submitted to the authorities by the manufacturer. By filing a CEP, the maintenance activities for the quality part of the registration dossier are facilitated. The updates of a CEP can be submitted by a quick and simple notification procedure, which is now regarded as an administrative procedure to change the dossier.

On the other hand, the MAH has no transparency on the content of and the changes to the substance stated in the CEP. Especially changes that might have an influence on the manufacturing of the finished product should be communicated by the CEP holder to the MAH in advance.

Condition no. 2 of the change of type IA no. 15 requires unchanged additional (to Ph. Eur.) specifications for impurities and product-specific requirements (e.g. particle size, polymorphic form) [2]. If a company wants to replace a manufacturer of the active substance by another or add an alternative manufacturer, the new manufacturer should produce in a way to fulfil these conditions. The last chemical reaction step of the manufacturing process and the following purification determine the impurity profile and the residual solvents in the active substance. As a consequence the manufacturing process of the old and the new manufacturer of the active substance should be the same at least on the last step. Otherwise the replacement of an active substance by a new manufacturer would require a type II variation.

Companies are always looking for additional suppliers for active ingredients of the same quality in order to stay flexible in their supply chain, to avoid out of stock situations and to assure the production of higher volumes of the medicinal product. After EU-enlargement these activities may increase, because there may be more MS included in a MRP and more markets have to be supplied with the medicinal product concerned.

Companies have to consider these conditions when a source change is planned to be implemented quickly and consequently should be filed in a quick type IA notification procedure.

It is however to be questioned how many manufacturers really exist that produce a particular substance in a way that condition no. 2 is fulfilled.

Even if a company has to choose between a manufacturer that fulfils condition no. 2 and others that do not, a cost-benefit analysis should be made as a basis to choose between the different suppliers.

For a company, the resources, costs and time to file a manufacturer, not complying with condition no. 2, by a type II variation have to be weighed up against the benefits that such a manufacturer might have, offering the substance for a lower price.

A close contact between the regulatory affairs department, quality control and supply chain management is recommended when deciding whether to accept a new supplier.

4.1.2 Major variations

Annex I does not list all changes that might be considered suitable for a notification procedure. All changes, not included in Annex I [2], are automatically classified as type II variations, even if these changes actually have to be considered as minor. That's why industry unions have suggested an "open box" for new categories of type IB variations. This suggestion has not been implemented into the new Variation Regulation, as it was considered to be unusual under EU law and it was not acceptable to the majority of the MS. It should be noted that according to Article 35 of Directive 2001/83 [10] (prior to amendment by Directive 2004/27 [19]) the *concept* of a minor variation has to be defined precisely. However, the article does not require the listing of every single change in Annex I [2]. It would have been possible and sufficient to define the concept of minor changes as a change that does not have an impact on quality, safety and efficacy of the medicinal product. Under this provision an open box would have been possible.

From industry's point of view, the rejection of the suggestion for an open box is a disadvantage. It makes the variation system in this point too schematic and rigid. Even if it can be scientifically demonstrated that a change, that is not listed in Annex I [2], has no impact on quality, safety and efficacy of a particular product, the change has to be filed as a type II variation. With regard to the time to implement the change and the fees that have to be paid for a type II variation, this issue represents a burden to industry.

4.1.2.1 Classification of changes to or addition of therapeutic indications as type II variation

According to the revised Variation Regulation all changes to a therapeutic indication or the addition of a therapeutic indication are classified as a type II variation. The revised Variation Regulation does no longer differentiates the changes of therapeutic indications by means of

the ATC-code, because it has been shown in the past that this differentiation was not always appropriate. Therefore, even the addition of an indication in a different therapeutic area or a change of the indication to a different therapeutic area no longer requires a new application for a MA. They are now classified as a type II variation [2].

The overall time for a type II variation procedure to modify the indication section is 120 days (clock-off period excluded) [20] and the change can be implemented in all countries after receiving the national approval of the revised SmPC. In comparison with the review time of an application for a new marketing authorisation (210 days), this represents a significant reduction of time needed for implementation.

With the new Regulation, research based companies may become more encouraged to perform clinical trials on additional indications, because the new development can be marketed in the enlarged EU earlier than before. The invested money in research and development can thus be compensated sooner.

Nevertheless, it is still possible to submit a full application for a separate marketing authorisation with a modified or a new indication, but under a different name and with a different SmPC for the medicinal product. This allows for business flexibility and keeps options for marketing strategies in the enlarged EU.

If the development of a new therapeutic indication is in line with the current marketing strategy of the medicinal product, the new therapeutic indication should preferably be filed as a type II variation.

If the development of a new indication offers possibilities for a new product's positioning on the market, then the option of filing a new application with a new name and SmPC for the medicinal product would have to be taken into account. The filing of a new application also has the advantage of allowing reconsideration of the markets to be included in the procedure. New MS of the enlarged EU can be included and markets with expected low sales can be excluded. According to Directive 2001/83 [10] it is possible for the MAH to withdraw the application in a particular MS, if this MS does not recognise the approval of a MA. According to *Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 amending Directive 2001/83 on the Community code relating to medicinal products for human use* [19], which has to be implemented into national law no later than 30 October 2005, withdrawal of applications will be possible as long as the coordination group is not involved in clarifying the divergences of the MS. When filing a type II variation, a withdrawal of the variation in some MS but not in others is not possible and the rejection of the new indication in a MS would trigger to refer the matter to the CHMP for arbitration.

If the new indication leads to a significant clinical benefit as compared to existing therapies and if it has been developed within the first 8 years after granting the MA, the data protection

period will be extended by one more year (Article 10 of Directive 2004/27 amending Directive 2001/83 [19]). This is advantageous to research based companies.

If the new development complies with a List B-Status of Council Regulation 2309/93 [21], a new full application for a MA can be submitted.

The deletion of an indication or a route of administration from the SmPC for safety reasons is no longer classified as minor variation. This change is now classified as a type II variation, because it has been shown in the past that the involvement of the CMS in the evaluation of this change is considered to be necessary. One reason for this is that the SmPC needs to be revised, deleting all listed issues in relation to the deleted indication, such as side effects and the dosage for example. Another reason for this classification could be the fact that a medicinal product with the indication under question should be available to patients who are dependent on this medicinal product and that there are no suitable alternatives. A deletion of this indication therefore needs to be evaluated through a type II variation procedure in all CMS, with regard to therapeutic alternatives in order to protect public health. A risk-benefit-assessment should be made in this case.

The classification as a type II variation will restrict the MAH in his freedom to decide to delete an indication or a route of administration for other reasons, e.g. for marketing issues. On the other hand, the MAH still has the possibility to withdraw the MA of the medicinal product or to stop the distribution at any time.

4.1.2.2 Medicinal products with biological active substances

The EU Variation Regulation provides specific provisions for variations to medicinal products with biological active substances. Whereas the former Annex I upgraded 7 type I variations for medicinal products with biological active substances to type II variations, the revised Annex I even includes 18 exceptions applicable to medicinal products with biological active substances that have to be filed as type II variations [2] *(see Table 1,2,3 in Appendix 2)*.

If the nature of the proposed variation and its consequences for a biological medicinal product are the same as compared to a medicinal product with a chemical active substance and if the variation is initiated by the manufacturer to apply for stricter limits on requirements, this variation should be classified in the same category independently of the kind of medicinal product, pharmaceutical or biological. A general classification of variations for biological medicinal products as a type II variation is considered to be too restrictive from industry's point of view. A more scientifically based approach would be highly appreciated.

4.2 Procedures and time lines

4.2.1 Submission of the variation

4.2.1.1 Allocation of the Mutual Recognition-Variation number

Following the experience gained, both by industry and MS and to simplify the procedural handling of variations, the MS have decided to place the allocation of the MR-Variation number in the hands of the applicant. From industry's point of view this approach is appreciated, because it is no longer necessary to contact the RMS to obtain a variation number. The new approach would prevent delays and saves time in the preparation for submission of a variation. *The MRFG Best Practice Guide for the allocation of the Mutual Recognition Variation Number for Type I Notifications and type II variations* [22] gives detailed guidance on how to correctly allocate the numbers. To characterise variations for medicinal products in the MRP in a unique and specific way, the MRP-number will be extended by two further elements: The change type (IA, IB, II) and a chronological number (Example: DE/H/0450/001/IA/001). Irrespective of the type of variation there is a continuous numbering system. The purpose of this chronological number to be counted on is to enable the MAH, the competent regulatory authorities or the supervisory authorities of the MS to get information about the history of changes of the medicinal product.

Due to this importance, the MAH should develop an appropriate system to follow-up on the numbering system for each MRP-product. It is recommended to keep the information on the MR-Variation number also in the internal change control system to ensure the tracking for changes with regulatory impact from their filing with the regulatory authority to the implementation in the plant. This documentation facilitates the preparation for an audit by supervisory authorities.

4.2.1.2 Submission principles

The suggestion from industry to introduce so-called "group variations", which means that a variation that affects multiple products can be filed in one single variation application, has not been implemented in the revised Variation Regulation. By contrast, the previous principle that a separate variation application has to be submitted for each change has remained unchanged. Where several variations have to be made, they have to be filed in parallel with a cross-reference to each other. Only consequential changes can be filed in one notification resp. application (Article 4 (2) (3), Article 5 (2)(3), Article 6 (2)(3) of CR 1084/2003 [2]).

From industry's point of view it would have been highly appreciated to have a more efficient procedure here, as especially in the enlarged EU, the number of countries participating

in a MR-variation procedure and as a consequence to be provided with variation packages, will increase.

With respect to changes that affect several products, a simplified approach for handling of variations has been introduced by the MRFG [23]:

If the MAH in case of a merger wants to change the name of the manufacturers and/or the name and address of the MAH (where the legal entity remains the same) in different concerned MS for a number of products in different strengths and pharmaceutical forms, it is possible to submit one variation per medicinal product (MA) including the changes due to the merger mentioned above. A simplified handling for variations, not related to a merger is also possible in the case of changes of a brand name (change no. 2 [2]) where the MAH wants to change the brand name after authorisation in more than one CMS or for a change in the name and/or address of a MAH where the name and or address is different in the CMS and the change is not be considered as a transfer. In such cases also the submission of only one variation per medicinal product will cover all different CMS. A discussion with the RMS on how to handle these issues is recommended before filing.

Especially in the light of the enlarged EU, this simplified handling of variations is highly appreciated. Mergers, brand name changes and changes of the name of the MAH are likely to occur frequently, because multinational companies will harmonise the enlarged EU market. Filing these changes in one variation decreases the regulatory workload tremendously.

4.2.1.3 National peculiarities

There are specific national requirements to be considered with the submission of the variation. *The Notice to Applicants Volume 2A Procedures for Marketing Authorisations, Chapter 7 General Information from July 2004* [24] gives detailed information for each MS and also includes the new MS of the enlarged EU.

Regarding the specific national language requirements, the revised Chapter 7 [24] states that the documentation for a type IA/IB notification and for a type II variation is now acceptable in English language in every country of the enlarged EU. This is advantageous to companies, because an English "core package" can be used for all EU-countries and as well for the multinational filing of variations. As a consequence, the translation costs will be reduced for companies.

However, with regard to the language requirements for the variation application forms, the number of samples to be provided for particular changes, the number of copies of the variation documentation to be provided and the time for payment of fees, there are still specific national requirements.

To cope with the administrative burden, companies are recommended to have in place a standard operating procedure for the handling of variations to medicinal products authorised through the MRP. The standard operation procedure should define and coordinate the steps to be taken by headquarter and affiliates to prepare and smoothly process a variation procedure from submission up to approval and implementation of the change. For the future, a harmonisation on submission requirements between the MS of the enlarged EU would be appreciated.

4.2.2 Notification procedure of type IA

The introduction of the type IA notification ("tell and do") for changes that do not affect the quality, safety or efficacy of the product or for administrative changes is generally appreciated by industry. All changes classified as type IA can be implemented more quickly [2] as compared to the previous Variation Regulation [4].

In fact, many of the minor changes are about modifications of the production process, the specifications and the test procedures of a medicinal product. These changes often result from ongoing refinement of the processes. For the MAH to be able to make a change in the production process, it is necessary to produce the product in the newly proposed way to generate the data that are necessary to support the change. It is appreciated being able to handle these minor changes as "tell and do" changes, because they have in fact already taken place or are about to take place. From industry's point of view, it is considered favourable, that the switch in production or in the analytical laboratory can almost be prepared in parallel to the submission of the variation. The production batches to be manufactured e.g. for validation of the new process can be sold with the almost entire assigned shelf-life after having received the acknowledgement of a valid notification after 14 days following submission of the notification. This will streamline the procedure for managing minor changes and increases the efficiency of a manufacturing plant.

However, this notification procedure also bears disadvantages. There is no information on the start of the procedure provided by the RMS. Companies have experienced that the RMS does not start the notification procedure right after the correct submission of the notification and this would cause a delay in implementing of the change.

There is no request by the RMS for clarification, information or documentation from the MAH and there is no clock-stop or suspension of the procedure. For the MAH that means that the documentation has to be complete when submitting, otherwise the notification would be rejected and the money spent on the fees is lost. The documentation for the notification should be prepared with the greatest care.

Article 4 (5) of CR 1084/2003 states, if the notification fulfils the requirements the competent authority of the RMS shall within 14 days following the receipt of the notification acknowledge the validity of the notification and shall inform the holder accordingly [2]. In legal

terms this means that as long as the MAH has not received a written acknowledgement, the variation cannot be considered as valid and thus cannot be implemented. As the number of minor changes and the corresponding workload of the authorities are expected to increase in the enlarged EU, it is uncertain if authorities will issue the acknowledgement in time. Therefore, a type IA notification should rather become a "true notification", effective or deemed to be valid by default at the end of the validation period, without any need for a formal acknowledgement. Industry would have appreciated an implicit approval to follow the "tell and do" approach. The time to implement a notification could even be reduced. Industry union EFPIA stated in their comments to the drafts of the Variation Regulations that the validation period of 14 days for a type IA notification is unreasonably long [25]. Taking into account the *Procedure for Automatic Validation for Mutual Recognition Procedures for Variations* of the MRFG Best Practice Guide [26] the overall time of the validation phase for a type IB notification is 10 days. This time line could be transferred to a type IA notification procedure as well, provided that no acknowledgement letter would be issued. There are still possibilities for optimisation of the type IA notification in the future.

MRFG recommends that each MS introduces a system of internal auditing to provide assurance of the validity of notifications *(MRFG Best Practice Guide for the Processing of Type IA Minor Variations (Notifications) in the MRP* [7]*)*. This auditing may comprise a detailed assessment of the supporting documentation against the conditions specified for type IA notification changes and also against the MAH's own checklist, which is appended to the application form. The outcome of the audit might be that the MAH is informed that a further submission (notification or variation) is required or that the matter has been referred to Inspectorate [7]. For industry this means that a notification might not be completed after the acknowledgement of a valid notification has been received. This leads to a fair amount of uncertainty in the industrial practice and actually questions the entire approach of "tell and do" changes.

4.2.2.1 Special situation in the acceded countries

After 1 May 2004, it is expected that the national variation procedures of the new acceded MS will follow the principles of the new EU variation procedures including the notification procedure of "tell and do"-changes. In some Eastern European countries (e.g. Czech Republic, Hungary) the Civil Service Act, however, does not recognize notifications. This turns out to be a bigger problem than initially expected, because the Ministry of Justice of these countries would not like to change the Civil Service Act. At the day of accession, the Variation Regulations have overcome this problem for medicinal products authorised by Community procedures (MRP, CP), but not for the national ones.

For example Czech Republic will manage the national variations in the same way as MR variations in the future, but the legislation still needs to be amended. The new decree on regis-

tration covering also the classification of variations (type IA, IB and II) has become valid as of 1 May 2004. To introduce also the new 14-day notification procedure, it will be necessary to change the Act on Pharmaceuticals, which will take some time. Hence, for national variations in the Czech Republic the 30-day procedure is also applicable for type IA variations at the moment. The Act will be changed in middle/end of 2005. But this date has not yet been confirmed (Information from Czech Agency, M. Smid, 15 March 2004).

This issue can also influence a company's strategy: By inclusion of the medicinal products of the new acceded MS in repeat-use procedures, instead of keeping national registrations of the medicinal product in these countries, the companies will benefit from the quick type IA notification procedure for minor variations and the implementation of these changes can take place at the same time in all EU countries.

4.2.3 Notification procedure of type IB

Due to EU enlargement, more MS will be involved in MR procedures and the subsequent maintenance activities in the future. Without the implementation of the new Variation Regulation, the decision making process during a variation procedure would have become even more difficult and time consuming. In order to avoid these difficulties, it was considered necessary to lay the coordination and evaluation of the type IB variation in the hands of the RMS on behalf of all CMS [2] [9]. In fact, this reflects a true mutual recognition and simplifies the procedure, as less correspondence between the RMS and the CMS is necessary during the procedure of a type IB notification. This modification leads also to a massive reduction of workload for the competent authorities of the CMS.

The MAH also benefits from this approach, because the MAH generally discusses the variation with the RMS prior to submission and is informed on the attitude of the RMS concerning the particular variation. This close communication is helpful, especially for complex variations where parallel notifications have to be filed. The MAH can design the notification documentation according to the requests of the RMS. Having the notification of type IB assessed only by the RMS will minimise the risk that the variation would be rejected or notified with grounds, as when all other authorities of the CMS would participate in this decision. A clear decision on a variation will be expected, which gives more assurance to the MAH in filing a variation and streamlines the notification procedure.

If the decision of the RMS is not shared by the CMS or is not favourable to the MAH, the issue can be referred to the CHMP for arbitration. As the MAH has the opportunity to discuss the notification with the RMS prior to submission, an arbitration triggered by the MAH is not to be expected. It would occur in cases of divergent opinions between the MAH and the RMS. It is questionable, whether a MAH would deliberately choose this long procedure of arbitration for a change of type IB, instead of resubmitting a new notification with amended docu-

ments. *Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 amending Directive 2001/83 on the Community code relating to medicinal products for human use* [19] introduces a new approach in the MRP and the decentralised procedure for the future. The coordination group is responsible for the examination of any questions relating to the MA of a medicinal product in two or more MS in accordance with these procedures (Article 24 [19]). The coordination group consists of one representative per MS (possibly accompanied by experts). Within the coordination group, all MS concerned shall use their best endeavours to reach an agreement. They shall allow the MAH the opportunity to make his point of view known orally and in writing. If the MS concerned fail to reach an agreement within a 60-day period, the matter shall be referred to the Agency for arbitration (Article 29 [19]). Unfortunately, this approach is not intended to apply to contentious issues of a variation procedure. It would have been appreciated to extend the scope of the coordination group to include contentious issues between MS concerning variations, because an arbitration procedure or a withdrawal of the variation application could be avoided and an agreement on contentious issues would be obtained. From industry's point of view this would be appreciated.

The time line of the notification procedure type IB [2] corresponds to that of the previous type I variation [4]. However, as now only the regulatory authority of the RMS is responsible for the evaluation, the time for evaluating the change could be reduced. For changes where the RMS has to contact the CMS, i.e. in case of a change in the name of the medicinal product (for clarification if there are no confusions) or in case of a change in pack size (to clarify reimbursement issues), a time line of 30 days is justified [9]. From industry's point of view, the time line for changes without CMS involvement is unreasonably long. This prevents industry from a faster implementation of changes in the manufacturing plant. A differentiation between type IB notifications with or without involvement of the CMS would have been appreciated.

4.2.4 Fees

At the beginning of the year 2004, many MS of the EU revised the regulations that determine the fees to be paid for variations. Some countries, like Germany and UK, have implemented different fees depending on the type of variation and on whether the authority acts as RMS or as CMS. For the CMS lower fees need to be paid. From industry's point of view, this approach is justified because the CMS takes a purely administrative role in the type IA and IB notification procedure. Despite the revision of their fee regulations, in some countries, such as Italy and the Netherlands, the same fee has to be paid irrespective of whether the authorities of these countries manage the variation as RMS or as CMS [27]. The payment of fees should follow the same approach in all MS of the EU and the MAHs should pay authorities a lower fee for managing a variation as a CMS. For the MAH, this would reduce the costs to be spent on variations.

4.2.5 Approval procedure of type II

The new approach for type II variations is, not to fix the time line of 60 days for the RMS to prepare the FVAR and the draft decision, but to differentiate the time lines for the assessment with regard to the particular matter of the change to be filed. Industry appreciates this new approach, as it is less schematic and allows for flexibility of the assessment time depending on the change and the urgency of the situation.

The 60 and 90-day time frames are maximum time lines, thus allowing for shorter procedures in particular situations [2] [20].

The RMS should agree with the MAH on the timetable for a variation depending on the particular type of change. The MAH may provide a draft of the variation application form and additional information to the RMS. The RMS should be informed of the background of the change and all details should be discussed prior to submission of the variation. A good preparation of the variation by the MAH and an open discussion with the RMS is therefore essential to facilitate the variation procedure and to guarantee a smooth implementation of changes. Even during the clock-off period, the RMS may liaise with the MAH as necessary in case clarification of the questions or responses is required. If there are grounds to extend the clock-off period, the RMS will give the new deadline to the MAH and inform the CMS accordingly [20]. For a successful filing of a type II variation, a good relationship between the RMS and the MAH is very important.

4.2.5.1 Type II variations with regard to safety issues

From industry's point of view, it is highly appreciated that variations concerning safety issues can be differentiated from the 60-day assessment time scale and can now follow an expedited procedure of 30 days [2] [20]. A quicker implementation of the change as compared to the former Regulation is the consequence and public health is protected to a greater extend.

It should be noted that the recommended time to give responses to a request for supplementary information in this expedited procedure is, with 10 days for the applicant, rather short [20]. In the case of an expedited procedure, the MAH therefore should mobilise capacities in the appropriate departments to be prepared to answer to the possible questions within the predetermined time frame. A good planning of resources with different departments in the company is therefore important prior to submission of the variation.

Before submitting a type II change concerning safety issues, the MAH is advised to contact the RMS in order to discuss the need for an urgent safety restriction (USR) compared to the expedited type II variation. With regard to public health, the distinction between an USR and a type II variation will probably controversially discussed between the authorities and the MAH.

Decisions concerning variations related to safety issues shall be implemented within a time frame as agreed between the RMS and the MAH in consultation with the CMS (Article 6 (11) of CR 1084/2003 [2]). This is a prerequisite for a harmonised, coordinated implementation of the variation in all MS concerned, which is important for the protection to public health. The MAH is responsible for the implementation. Especially for safety issues, the MAH should prepare an internal implementation plan to document all actions in the appropriate departments to implement the change within the agreed time frame. If the change is not implemented in time and the lack of implementation of the change causes harm to a patient, the causality assessment in a legal procedure, could lead to the result that the company is liable. For these cases, the companies could lose their insurance cover. Therefore, MAHs should treat the implementation of changes regarding safety issues with carefulness.

4.2.5.2 Type II variations regarding chemical-pharmaceutical changes

The Regulation states that the RMS should close the procedure and notify the CMS and the MAH of the outcome of the variation procedure, implying that the variation can be implemented from this notification (Article 6 (9) of CR 1084/2003 [2]). The MS have agreed that best practice is that where the variation application results in changes to the SmPC, labelling and packaging leaflet/insert the MAH should wait for individual CMS approval. In cases where the variation does not impact on the SmPC, labels and packaging leaflets/inserts the changes can be implemented in the CMS at the completion of the variation procedure as notified by the RMS [20]. This is an advantage for type II variations amending the chemical-pharmaceutical section of a dossier (Module 3 of the CTD dossier) and not influencing the above-mentioned product information of the medicinal product. Pharmaceutical companies, especially manufacturing sites, do not need to wait for national approvals of each concerned Member State of the enlarged EU. As soon as the procedure is closed by the RMS (Article 6 (9) of CR 1084/2003 [2]) the change can be implemented for all concerned MS at the same time. This leads to a reduction of the logistic burden to a manufacturing facility. Compared to the former Variation Regulation, for example, it is no longer necessary to release the product according to two different specifications until the approvals of all national authorities have been issued in all concerned countries of the EU.

For changes amending the chemical-pharmaceutical section of the dossier, this approach is in line with the variation procedures of type IA and IB. This is highly appreciated by industry, especially as the number of the MS to be included in a MR variation procedure will increase in the enlarged EU.

The implementation of changes in a multinationally operating company, which manufactures products for many markets in the enlarged EU, will be more efficient than before.

4.2.5.3 MAH has the right to arbitration

An added advantage for industry is now, that the MAH can apply for arbitration within 10 days of the end of the procedure in cases in which the variation application is rejected. The MAH has now the same right to arbitration as the CMS.

For complex type II variations it would be useful to have the possibility to refer the contentious issue of a variation to the coordination group for an agreement and only if no agreement is achieved, the matter should be referred to the Agency for arbitration. This could lead to an agreement on a contentious issue between the MS concerning a variation and an arbitration procedure or a withdrawal of the variation could be avoided. From industry's point of view, it would be highly appreciated to include contentious points of a variation procedure to the scope of the coordination group in the future. (*Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 amending Directive 2001/83 on the Community code relating to medicinal products for human use* [19]).

4.2.6 Urgent safety restrictions (USR)

The definition of an USR has been amended to an interim change to the product information concerning particularly one or more of the following items in the summary of product characteristics, the indications, posology, contraindications, warnings, target species and withdrawal periods, due to new information having a bearing of the safe use of the medicinal product (Article 3 (5) of CR 1084/2003 [2]). The term "particularly" is understood as "specifically" in all EU-legislation. Compared to the old definition of an USR, not including this term, the new definition opens an USR to all issues having a bearing on the safe use of the medicinal product. This is appreciated with regard to the protection to public health, but the MAH now obtains more responsibility in making the decision of an issue as to have far-reaching consequences on the safe use of the medicinal product. Therefore, all information in drug safety has to be assessed and documented very carefully.

The MAH is obliged to immediately inform the competent authorities in the event of a risk to public or animal health. If the concerned authorities have not raised any objections within 24 hours following receipt of this information, the urgent safety restriction is deemed to be accepted (Article 9 (1) CR 1084/2003 [2]). This 24-hour period takes place after an initiation phase and a pre-submission phase. (*MRFG: Standard Operation Procedure: Urgent Safety Restriction* [28]). Prior to the submission of the USR application, the MAH is advised to contact the RMS in order to discuss the need for an USR and to prepare the requested documents, especially the revised SmPC and the "Dear Doctor Letter". Before starting the 24-hour period, the RMS should send all available information to the CMS via the rapid alert system (initiation phase). If consensus cannot be achieved between the MS regarding the imposed USR, the matter could be considered by the Pharmacovigilance Working Party (PVWP). In this case, an

additional meeting could be organised by the PVWP. The timetable for submission of the USR is agreed on between the MAH and the RMS and is communicated to the CMS (pre-submission phase). Neither the MRFG guidance [28] nor the CR 1084/2003 [2] specifies how much time should be spent on the initiation phase and pre-submission phase. This is especially of relevance if no consensus can be achieved between the RMS and the CMS on the issue on which it is intended to impose the USR. As more MS will be included in a MRP in the enlarged EU, divergent opinions regarding a safety issue are more likely to occur, so that the PVWP might be more often involved in the future. From industry's point of view and with regard to the protection of public health a defined procedure with a definite time line for the initiation phase and the pre-submission phase should be provided, which should also include the participation of the PVWP to reach a consensus. This procedure should also include details as to when national actions can be imposed on the MAH until the type II variation procedure is finalised.

The information on the matter imposing an USR is available to the RMS and the CMS before the submission of the USR and the start of the 24-hour period. With regard to this fact and to the protection of public health, it is hard to understand that this 24-hour period excludes Saturdays and Sundays and recognised public holidays, although public holidays are not harmonised within the enlarged EU. As a consequence, the 24-hour period can be extended, thus leading to a risk to public health. The 24-hour period should be a fixed period, not excluding Saturdays, Sundays and recognised public holidays.

The fact has been newly introduced that the USR shall be implemented within a time frame as agreed with the competent authorities. In the former Variation Regulation 541/95 [4] a due date of 24 hours for implementation had to be followed. This innovation can be considered as a positive modification from the industrial point of view, because it has been shown in the past that a 24-hour deadline for implementation of the USR is not always practical. Deciding on the time frame in a case-by-case setting, will allow a realistic implementation time adapted to the severity and urgency of the issue imposing the USR. The MAH is responsible for the implementation and should treat this task with carefulness in order to avoid any harm to patients for which the MAH could be liable.

In contrast to the former Regulation, the time line for the corresponding type II variation reflecting the USR is now specified. The MAH has to submit the application for the type II variation, including the appropriate documentation, immediately and in any case no later than 15 days after the initiation of the USR (Article 9 (2) of CR 1084/2003 [2]). Until this type II variation is finalised, the interim SmPC should be considered as the current version.

This time line of 15 days seems quite short in which to prepare a complete documentation for a type II variation. Companies requests that it should be possible to extend this time line with the RMS`s consent and in accordance with the safety aspect concerned and the documen-

tation to be prepared to support the change. As the interim SmPC is valid to prevent further risks, it should be possible that an appropriate time could be spent to prepare a reliable documentation.

The content of the corresponding type II variation should be in agreement with the RMS. It is very important that the competent departments in the company are informed on time to prepare the appropriate documentation for the submission of the variation; preferably on the day the issue is addressed to the RMS to impose an USR.

All administrative work for the submission of the variation has to be prepared simultaneously (e.g. copies, translations, payment of fees). The administrative burden to be coped with in this narrow time frame will increase, because more countries of the enlarged EU will be involved in the procedure. A simplification of the submission requirements for the type II variation following an USR would have been appreciated from industry's point of view.

For companies, it is necessary to develop a standard operation procedure to lay down an internal schedule to be used in case of an USR defining the main tasks, responsibilities, time lines and the cooperation with the affiliates.

4.2.7 Extension applications

The revised Variation Regulation officially introduces the term "extension". An extension of a MA fulfils the conditions set out in Annex II to the Regulation (Article 2 of CR 1084/2003 [2]). Annex II lists the changes to a MA requiring an extension application. This approach follows the definition of a MA to cover all strengths, pharmaceutical forms, administration routes, presentations as any variations and extensions to be granted an authorisation or be included in the initial MA. All these MA shall be considered as belonging to the same global MA. (Article 6 *Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 amending Directive 2001/83 on the Community code relating to medicinal products for human use* [19]). This harmonises the term of the MA in the EU.

An extension of a MA has the same invented name and SmPC as the initial MA apart from the inclusion of a subsidiary term into the name according to the *Guideline on the SmPC* [12] to allow the differentiation from the existing medicinal product. For an extension application, the MAH must be the same as the MAH of the existing MA. However, it is still possible to submit a separate, full application for a marketing authorisation, which has already been authorised, but under a different name and with a different SmPC (Aim of the Regulation (8) of CR 1084/2003 [2]).

This enables flexibility to perform marketing strategies and to market a new development under a new brand name or still in line with the already marketed brand name of a medicinal product. This flexibility is advantageous to the pharmaceutical industry.

The option of submitting an extension application does not exist, if the conditions set out in Annex II [2] are not met. Then a new application with a different brand name has to be provided.

For example: Changes to the active substance (Annex II No. 1 (i)-(v)) can be filed as extension applications under the condition that the safety and efficacy characteristics are not significantly different [2]. The therapeutic moiety of the active substance has to remain the same. This has to be demonstrated by the applicant by performing studies to show equivalence. If this issue cannot be demonstrated or the active substance is a new active substance (Definition NTA, Volume 2A Chapter 1 [30]), the change has to be classified as a new application.

4.2.7.1 Granting of extension applications

An extension to or a modification of the existing marketing authorisation has to be granted by the competent authorities [2]. The MRFG guidance *Application under Annex II of Regulation (EC) 1084/2003 from January 2004* [31] provides detailed information.

The MA of the initial product has to be based on any legal basis according to Directive 2001/83 [10]. That means a stand-alone application, informed consent application, generic application or a fixed combination can be the basis for an extension application. Without prejudice to the provisions of Annex II of CR 1084/2003 [2], an application for a line extension should be made in accordance with the provisions of Article 8 and Article 10.1 of Directive 2001/83 [10], but it can contain references to the documentation of the initial MA, instead of a resubmission of the data. References to toxicological and clinical studies of the initial application are possible by providing bridging studies showing the compliance of the extension with the initial medicinal product. The documentation to be submitted is therefore of less volume as compared to a new, initial application. This is advantageous to both industry and authorities.

The MAH is advised to contact the RMS for general recommendations on the documentation to be submitted.

CR 1084/2003 [2] is not applicable to independent national MAs, which have not benefited from any Community procedure. However, as mentioned in the *Commission Communication 98/C229* [32], extensions of national MAs cannot be excluded from the scope of mutual recognition. Therefore, for situations where the originator product was granted MAs through independent national procedures only, both national and MRP are acceptable on a voluntary basis of the applicant. To allow more flexibility the MS reached agreement that parallel national and MRP are also acceptable for the same product and that parallel MRP are also acceptable [32].

This is of importance regarding the products authorised in the new countries of the enlarged EU. It is not mandatory to include the national MAs of the acceded countries in a MRP after 1 May 2004. Nationally authorised MAs in these countries that comply with all EU requirements and that are based on an upgraded dossier, can stand alone and even in parallel with the same product approved in a MRP for other MS of the former EU. For extensions of originator products authorised through a mixture of both, national and mutual recognition procedures depending on the MS, there are the following procedures for filing an extension:

The mutual recognition procedure has to be followed for line extensions of originator product authorised through the MRP.

Both procedures, national and MR are acceptable for line extensions of originator products authorised nationally, meaning that parallel national and MRP are acceptable in this case.

For nationally authorised products, the companies can choose their filing strategy by staying national or adopting the possibility to include the extension into the MRP. When choosing the latter option, the applicant would have to harmonise the already approved national SmPC with the MR SmPC in order to support the applications in all concerned MS with the same dossier (*Commission Communication 98/C229* [32]). It has to be noted that in case of withdrawals during the MRP there is no possibility anymore to resubmit a national procedure. Companies have to take these facts into consideration, when choosing the procedure.

4.3 Filing the dossier and variations

4.3.1 Impact of the CTD format on performing variations

Filing a registration dossier in format of the Common Technical Document (CTD) was intended to be valid from 1 July 2003. But it became mandatory from 1 November 2003, because from this date the revised Annex I of Directive 2001/83 [10] was implemented. Since 1 November 2003 all variation applications have to be submitted using the CTD format. This format requirement is also applicable to changes to the EDMF.

The Notice to Applicants, Volume 2 B has listed Questions and Answers concerning the CTD format [33]. In this Question and Answers section, it is explicitly stated that there is no obligation to reformat the dossier of already authorised medicinal products into the new EU-CTD format. For variation applications submitted using the CTD format, cross-reference to old EU-format documentation will be accepted. Clear references to any old format documentation are essential. Applications for extensions must also be submitted using the new EU-CTD format. Reference can be made to the already assessed and authorised old parts of the dossier, but only if no new additional data are submitted in these parts.

Any new data (either additional or revised) in support of the variation must be submitted using the CTD format. If data need to be submitted that are unchanged (e.g. copy of approved specifications), the MAH has to provide a declaration that the content of the reformatted documents is unchanged.

Until 30 April 2005 repeat-use procedures will be acceptable in the old EU-format, if the original submission of the dossier in the RMS was made before 1 July 2003. If the applicant has already filed variation applications in the CTD format, this documentation can be annexed in the CTD-format to the existing dossier in the old EU-format. In these exceptional cases a mixture of formats within the same part will be accepted, but quality data should be reformatted as soon as possible. If the repeat-use procedure is started after 1 May 2005 it is an obligation to submit all quality data in the CTD-structure (*Questions and Answers of NTA Volume 2 B about the CTD from June 2004* [33]). It is expected that the number of repeat-use procedures will increase after EU-enlargement to include the newly acceded countries to the MRP and to market the product with a harmonised SmPC in the entire EU.

However, to facilitate the handling of the variations and extensions in the future and in order to maintain an appropriate and logical documentation to be suitable for further variations, companies should be encouraged to deliberately reformat the quality part (part II) of their product dossiers into the CTD-format of Module 3. The submission of reformatted documentation should preferably occur simultaneously with, but separately from, the submission of the variation. As the case may be, a clear distinction between reformatted (unchanged) information and the documentation supporting the simultaneously submitted variation should be made.

It is recommended that the reformatting of the quality part of the dossier should be a major objective for the regulatory affairs department and should be triggered by the planned regulatory activities, such as repeat-use procedures and variations. Time, human resources and costs for reformatting the quality part should be included in the budget.

4.3.2 Impact of the regulatory information in a dossier on performing variations

A variation is an amendment to the contents of the documents referred to in Articles 8 to 10 of Directive 2001/83 (Article 3 of CR 1084/2003 [2]). These documents form the legal basis for the MA of a medicinal product, submitted to the competent authority. As a rule amendments to documents/details, which are not part of the documentation for the MA, do not trigger a variation.

The CR 1084/2003 [2] provides some advice on how to properly decide on the content of the documentation that is to be included into a registration dossier:

In the preface to Annex I, it is stated that there is no need to notify the competent authorities of an updated monograph of the Ph. Eur. or a national pharmacopoeia of a MS in case that the compliance with the updated monograph is implemented within six months of its publication and reference is made to the "current edition" in the dossier of an authorised medicinal product. To avoid unnecessary variations, the applicant should not include the edition number of the Pharmacopoeia or a copy of the monograph of the Pharmacopoeia into the dossier. Companies should follow this recommendation in order to reduce the regulatory workload and save money that would otherwise be spent for unnecessary variations.

Annex I of CR 1084/2003 [2] does not mention changes to the batch size, the manufacturer or the retest period for excipients. Consequently, if corresponding information has been included to the dossier and needs to be changed, this change cannot be classified as a minor variation. It is therefore advisable for the MAH not to include this kind of information into the registration dossier, because it is not required by quality guidelines to do so.

If this information is part of the registration dossier and a change occurs, this change would be classified as a type II variation. The preparation of a type II variation would bind human resources and result in high unnecessary costs. This fact should be considered for the preparation of the quality part of the dossier.

5 Discussion of the impact of Commission Regulation 1085/2003 on the industrial practice in performing variations with regard to the EU enlargement

The MAs of centrally authorised products have become valid in the ten new MS at the day of accession and consequently the number of countries participating in a variation procedure and falling under the scope of the Variation Regulation CR 1085/2003 [3] is twenty-eight in total, resulting from twenty-five MS of the EU and three countries of the EEA (Norway, Iceland and Liechtenstein). Industry and authorities therefore appreciate a rational variation system.

The above discussion regarding the classification of variations, the procedures and time lines holds also true for CR 1085/2003 [3], except that for variations according to CR 1085/2003 [3] only one authority, the EMEA is involved. In the current chapter, the main focus will be on the differences and particulars of CR 1085/2003 and its impact on industrial practice in performing variations on centrally authorised products.

To take the preliminary steps for a variation, applicants are advised to consult the detailed procedural guidance on handling of variations as published in the *EMEA Post-Authorisation guidance Human Medicinal Products* [8]. Compared to the previous guidance, the fact remains unchanged that applicants are still strongly recommended to inform the EMEA and the (Co)-Rapporteur of all upcoming post-authorisation submissions for the following 6-12 months, in order to allow optimal planning, identification of procedural issues and handling of overlapping applications. For the companies, that means that even minor type IA variations that are subject to a "tell and do" change should be planned 6-12 months in advance for a centrally authorised product.

From industry's point of view, it is expected that despite having to pre-inform the EMEA of all upcoming variations, there should be flexibility to file upcoming variations without notifying the EMEA in advance if the change requires a quick implementation. Otherwise, the procedure would not comply with the "tell and do"-principle. Companies should address this issue to the EMEA.

Even prior to accession, for variations of a centrally authorised product that were based on new clinical studies, copies of these variations were sent to the, so-called "Observers" of the accession countries that were named by the former CPMP (now CHMP). This has been advantageous to authorities of the new MS, which have sent members to the Agency's scientific committees from 1 May 2004. They could prepare themselves early for centrally authorised products that have become authorised in the new MS from 1 May 2004. Companies benefit from this approach as well, having scientific committee members of authorities in the acceded countries being familiar with their centrally authorised products.

In case a variation affects the SmPC, labelling and/or package leaflet, the affected revised product information Annexes to the Commission Decision have to be submitted. The English language version has to be submitted as a paper version for one relevant example and electronically a complete set of Annexes for the English version and for all other languages have to be provided. As of April 2004, the complete set of Annexes should include the 9 additional accession country language versions for notifications resp. variations affecting the product information [8]. An early integration of these countries into the variation procedure, which provide for translations of product information, is appreciated to be prepared for a centrally authorised product in the enlarged EU.

Since EU enlargement, companies have to cope with an increased number of translations of the product information when performing variations, even if the product is not planned to be marketed in some of the MS. But on the other hand, the enlarged EU obtains the advantage for companies to have, from one day to another, a registration for an extended market for all centrally authorised products, which includes the possibility to reconsider marketing strategies.

5.1 Change in name of a centrally authorised medicinal product

For centrally authorised medicinal products, the number of name changes will probably increase in the enlarged EU. The system of Community Trademarks (CTMs) will be transposed to the acceded countries, as will Community designs. To counter the difficulty of prior rights of existing trademarks in the new MS of the EU, there are also provisions in the treaty stating that prior rights obtained in good faith in the new MS must be respected. Where there is a prior right in a new MS, the CTM will not be valid. Pharmaceutical companies have to consider the impact of any existing trademarks on these new markets [34]. Some names are not suitable for the medicinal product in the new MS, as they cannot be pronounced or have a different meaning. A name change of the medicinal product will be the consequence. It is expected that the number of changes according to Annex I no. 2 of CR 1085/2003 [3] will increase. When a name change is planned, the EMEA makes a check on the acceptability of the new name of a medicinal product by the MS. If the name is considered acceptable, the EMEA issues a letter of acceptance. This should be finalised before the variation is submitted. An evaluation of the name change is therefore not required anymore during the variation procedure. From industry's point of view this change should be filed as a type IA notification and the classification as a type IB notification clearly is of disadvantage for industry.

5.2 Update of the MA every 6 months

For minor variations of type IA and IB, the Commission shall where necessary, and based on a proposal prepared by the EMEA, update every 6 months the marketing authorisation (Ar-

ticle 4 (5), 5 (7) of 1085/2003 [3]). However, the MAH should bear in mind that type IA and IB variations affecting the product information Annexes to the Commission Decision can be implemented in the companies without awaiting the 6-monthly update of the MA (*Notice to Applicants, Chapter 5 Variations* [35]). Therefore, this approach is not a disadvantage for the MAH.

While the practicality of the Commission updating the MA every 6 months is understood as a means of reducing the administrative burden to the Commission, it may have the following implications on industry regarding the EMEA certification. This is discussed in the following chapter.

5.2.1 EMEA certification

The EMEA issues certificates of a centrally authorised medicinal product in conformity with the arrangements laid down by the WHO. These certificates confirm that the product is authorised in the EU. Besides, the good manufacturing status of medicinal products is certified. These certificates are intended for use in support of marketing authorisation applications in and export to non-EU countries.

The EMEA certifies the MA as amended by Commission Decision. Without an updated MA, it would not be possible to obtain an updated EMEA Certificate of Medicinal Product. A multinationally working company wants to implement a variation on a global basis. For several non-European countries an updated EMEA Certificate is needed for filing variations, especially for changes that lead to a revised SmPC, that introduce changes to the manufacturer of the dosage form or to the composition of the medicinal product. To find a solution for the issue that the Commission updates the MA every 6 months for minor variations, the EMEA amended the procedure for the certification of medicinal products *(EMEA/25057/03 What's new for EMEA Certification of Medicinal Products from 1 October 2003* [36]). The EMEA excludes minor variations of type IA and IB, which are endorsed by the EMEA from the provision to certify the MA as amended by Commission Decision [36]. On the application form for obtaining the Certificates, companies have to indicate all information on recent variations of particular importance to the EMEA Certificate. If this information on completed variations is missing, the EMEA will certify the latest status of the MA as approved by Commission Decision. Companies have to pay attention to get the Certificate updated including all concerned variations, otherwise the Certificate does not reflect the current status, which may cause problems when filing variations in non-EU countries. Therefore companies should take the responsibility for having a suitable system to follow-up on the variations of their medicinal products.

6 Discussion of the impact of the Commission Regulation 1084/2003 and 1085/2003 on the industrial practice with regard to the multinational procedure in performing variations

When planning variations on a globally marketed product, different demands on documentation and different time lines for the implementation of the change in different countries have to be taken into consideration. The regulatory affairs department has to plan the strategy of filing variations in co-operation with the appropriate departments of a facility (e.g. logistics, manufacturing, quality control) in order to streamline the procedure as far as possible to ensure a smooth implementation of a change to a medicinal product for all countries.

To decrease the logistic burden, it would be highly appreciated to have less variety of data requirements and time line differences for a particular change in different countries.

A company could work more rationally, if common data repositories for preparing variation packages could be used that are suitable to meet the requirements of at least the main global markets.

This chapter should compare the time lines and data requirements of the revised EU Commission Regulations with the procedures in performing variations in the industry regions USA and Japan in order to assess their suitability for a multinational variation procedure with focus on the three main industry regions and considers the industry's point of view.

6.1 Comparison of the revised European variation system with the procedure of post-approval changes in the USA

Section 506A of the US Food Drug and Cosmetic Act (FD&C Act [40]) and § 314.70 (21 Code of Federal Regulations (CFR) 314.70 [41]) differentiates between 4 reporting categories for changes. The US system differentiates between minor (Annual Report), moderate (Change Being Effected (CBE), Change Being Effected 30 (CBE30)) and major changes (Prior Approval Supplement (PAS)) whereas the EU system distinguishes between minor and major changes leading to 3 change reporting categories (IA, IB, II). The FDA published an April 2004 guidance document *Changes to an Approved NDA and ANDA* [42] providing explanations for the reporting categories in detail. Table 4 gives an overview on the system of post-approval changes in the US as compared to the variation system in the EU.

Table 4 Comparative overview of classification of changes and time lines of the EU and the US

Change type	EU	US
MINOR	**NOTIFICATION PROCEDURE** • **Type IA:** Implementation of the change after 14 days TELL AND DO • **Type IB**: Implementation of the change after 30 days TELL, WAIT AND DO → change classification according to CR 1084/2003 and 1085/2003: change listed in Annex I which fulfils the conditions set out therein	**DESCRIPTION AND DATA IN** • **Annual Report**: Implementation of change immediately DO AND TELL → change classification according to SUPAC: **level 1** unlikely to have any detectable impact on formulation quality and performance
MODERATE	Not available	**NOTIFICATION WITH AND WITHOUT A WAITING PERIOD** • **CBE**: Implementation of the change upon submission to the FDA TELL AND DO • **CBE 30**: Implementation of the change after 30 days TELL, WAIT AND DO → change classification according to SUPAC: **level 2** could have a significant impact on formulation quality and performance
MAJOR	**APPROVAL PROCEDURE** • **Type II variation** TELL AND WAIT Overall procedure of 120 days for changes to or addition of indication or non-food producing target species Overall procedure of 30 days with regard to safety issues. Overall procedure of 90 days for all other type II changes (e.g. to CMC section) → change classification according to CR 1084/2003 and 1085/2003: change which cannot be deemed to be a minor variation or extension application	**PRIOR APPROVAL** • **PAS**: Review cycle 4- 6 months or expedited review TELL AND WAIT → change classification according SUPAC: **level 3** likely to have a significant impact on formulation quality and performance • Supplements for new indications of approved drugs **Efficacy supplement** Review time: approx. 10-12 months **Priority Efficacy supplement:** Review time: 6 months
NEW APPLICATION	• **Extensions** require a new application Annex II of CR 1084/2003 and 1085/2003: - Change to the active substance - change to pharmaceutical form, strength, route of administration - change or addition of a food producing target species	• **New NDA** - change of active ingredients - route of administration - dosage forms - strengths/concentrations, or - excipients

6.1.1 Minor changes

According to the US system, a minor change is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity or potency of the product. In contrast to the EU variation system, in the US, minor changes are grouped together and the applicant has to describe these changes in the next **Annual Report** (§ 314.70 (d) [41]). These minor changes can be implemented immediately and are also called "do and tell" changes [42]. The EU variation system does not have this kind of reporting procedure.

6.1.2 Moderate changes

A moderate change has a moderate potential to have an adverse effect on identity, strength, quality, purity and potency of the product as these factors may relate to the safety and effectiveness of the product. There are two types of moderate changes:

Supplement-Change Being Effected 30 (CBE 30) (§314.70 (c) (3) [41]): A submission of a supplement to the FDA is required at least 30 days before the distribution of the drug product made using the change. The drug product made using a moderate change cannot be distributed if the FDA informs the applicant within 30 days of receipt of the supplement that a Prior Approval Supplement (PAS) is required. For each change, the supplement must contain information determined by the FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change. If the FDA informs the applicant within 30 days of receipt of the supplement that information is missing, implementation of the change and distribution of the product must be delayed until the supplement has been amended to provide the missing information [42]. The change principally corresponds to the type IB notification of the EU variation system as far as the time line is concerned. Both comply with the "tell, wait and do" procedure.

Supplement-Change Being Effected (CBE) (§314.70 (c)(6) [41]): A change submitted under a CBE may be implemented upon submission of the documentation to the FDA. In contrast to the EU procedure for a type IA notification, this procedure is a real "tell and do" procedure, because no waiting period of 14 days for the acknowledgement of a valid notification is necessary.

If the FDA disapproves a CBE 30 or CBE supplement, the FDA may order the manufacturer to cease distribution of the medicinal product that has been made using the disapproved change [42].

6.1.3 Major changes

A major change is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a product as they may relate to the safety or effectiveness of the product. A major change requires the submission of a **Prior Approval Supplement (PAS)** (§314.70(b) [41]). The review cycle for a PAS is 4-6 months. An applicant may ask for expedited review in case of public health reasons or if a delay in making the change would impose an extraordinary hardship on the applicant [42].

Compared with the EU variation system, the time line for a PAS is longer than that for a European type II procedure for major variations. Especially the handling of changes to or addition of indications as a type II variation with an overall procedure of 120 days (without clock-stop) for the review time is faster than the review time of an efficacy supplement (10-12 months, priority efficacy supplement 6 months *Guidance for Industry: Standards for the Prompt Review of Efficacy Supplements, Including Priority Efficacy Supplements from May 1998* [43]).

6.1.4 New NDA

Because NDA supplements are reviewed faster and have lower user fees than new NDAs, the difference between both is important. Briefly, new NDAs are required when any of the following changes occur: active ingredients, routes of administration, dosage forms, strengths/concentrations, or excipients. A NDA supplement is used when the drug change involves the composition of the approved product or a new indication to an approved product [27].

6.1.5 Comparability protocol

A comparability protocol is a detailed prospective plan on the evaluation of product-specific changes on e.g. manufacturing processes, equipment or analytical techniques. The comparability protocol is based on a comparison between the new and the old procedure. The objective of a comparability protocol is to show that the planned change has no negative influence on the medicinal product with regard to identity, purity and quality. A comparability protocol should be submitted as a PAS and therefore will be approved by the FDA. The advantage is that the comparability protocol can be used to reduce the reporting category for the specified change and for changes that are similar (changes of repetitive nature) [44]. That means that future changes do not need to be filed as a PAS, but can be filed as a CBE 30, CBE or AR. The FDA published a guidance document named "*Comparability Protocols-Chemistry, Manufacturing and Controls Information from February 2003* [45], which is available as a draft document. This scientifically based approach in the classification is not known to the European variation system.

6.1.6 Documentation requirements

Documentation requirements for changes are laid down in the scale-up and post-approval changes (SUPAC) guidances issued by the FDA (CDER). In contrast to the EU, where the documentation requirements for a change are listed in one document (*Guideline on Dossier Requirements for Type IA and IB Notification* [6]), the documentation requirements for filing a change in the US are listed in SUPAC documents that are issued for different dosage forms. That means that the documentation requirements are adapted to the specific features of the different dosage forms. SUPAC guidances exist for immediate release solid oral dosage forms (SUPAC-IR [46]), modified release solid oral dosage forms (SUPAC-MR [47]), and nonsterile semi-solid dosage forms (SUPAC-SS [48]). For transdermal delivery systems (SUPAC-TDS) the guidance is in preparation. For immediate release and modified release solid oral dosage forms and nonsterile semi-solid dosage forms, there exists a manufacturing equipment addendum [49] [50]. The SUPAC guidelines classify the level of a given change depending on its likeliness to have any detectable impact on formulation quality and performance.

The guidance on bulk actives post-approval changes (BACPAC) divides the manufacturing process of the drug substance into two parts. BACPAC I [51] covers changes made from the beginning of synthesis up to the final intermediate. BACPAC II covers changes to the final intermediate specifications and changes made after the final intermediate (last step). The BACPAC II guidance is still in draft. Also in preparation is the guidance for industry on analytical methods post-approval changes (AMPAC).

The SUPAC and BACPAC guidances provide the framework of documentation requirements. However, the applicant is strongly advised to discuss the documentation requirements for each specific change with the FDA prior to filing the change.

6.2 Comparison of manufacturing transfers between EU and US system for post-approval changes

Manufacturing transfers with regard to the replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product, are managed as minor variations according to the EU variation system under the condition (besides others) that the site is appropriately authorised to manufacture the pharmaceutical form or the product concerned and that a satisfactory inspection has taken place in the last 3 years (change no. 7 of CR 1084 / 2003 [2] and CR 1085/2003 [3]). If these conditions cannot be fulfilled, this change has to be regarded as a major change. The US system follows a similar approach by classifying manufacturing transfer changes without satisfactory cGMP inspections for the type of operation as a major change, requiring a PAS (*Changes to an Approved NDA and ANDA* [42]).

In the following tables, a comparison between the US and the EU is given for managing manufacturing transfers of an **immediate release solid, oral dosage form**.

Replacement or addition of a manufacturing site for secondary packaging

Table 5 Comparison of EU and US requirements for replacement or addition of a manufacturing site for secondary packaging

Country	Change classification / approval time	Conditions	Documentation to be prepared by the MAH
EU	IA, 14 days TELL AND DO	• satisfactory inspection in the last 3 years • site appropriately authorised to manufacture the product concerned [2]	• copy of current manufacturing authorisation (if site is in the EEA) • date of the last satisfactory inspection • variation application form should clearly outline the present and the proposed manufacturer [6]
USA	Annual reportable 0 days (check) DO AND TELL	• Satisfactory cGMP inspection	• The FDA should be notified about the different site and its satisfactory inspection in the summary section of the AR; a full description with identification if the site is a replacement or an alternative has to be made.[1] • Further information as determined by the FDA to make a proof on equivalence between the old and the new secondary packaging site.[1]

[1] *Changes to an approved NDA or ANDA; For secondary packaging, the potential for adverse effects of the drug product is considered to be independent of the type of the drug product dosage form. Therefore no SUPAC guidance can be considered.*

This example shows that the conditions and documentation requirements are very similar in the EU and the US. In both regions the change in the manufacturing site for secondary packaging is classified as a minor change. Hence, the applicant can prepare one core package containing all information required for the EU variation that should be discussed with the FDA. This is an advantage if variations have to be filed multinationally. The FDA requires the applicant to demonstrate equivalence between the old and the new secondary packaging step. Therefore the FDA might require the documentation of the EU to be supplemented by batch analysis data.

The difference between the EU and the US system concerning this variation is that the MAH can implement the change immediately for the US market without the necessity of preparation and submission of a variation beforehand. This is of an advantage and improves

logistic flexibility at the manufacturing site and makes the switch in the facility for secondary packaging easier. To decrease the logistic burden, it can be useful for companies to set the implementation of the transfer of secondary packaging for the EU and US markets together on the date of receiving the acknowledgement of the valid type IA notification for the EU countries.

Replacement or addition of a primary packaging site for an immediate release, solid oral pharmaceutical form (e.g. tablets and capsules)

Table 6 Comparison of EU and US requirements for replacement or addition of a manufacturing site for primary packaging

Country	Change classification / approval time	Conditions	Documentation to be prepared by the MAH
EU	Type IA, 14 days TELL AND DO	• satisfactory inspection in the last 3 years • site appropriately authorised to manufacture the product concerned • product concerned is not a sterile and/or biological product [2]	• copy of current manufacturing authorisations (if site is in the EEA) • date of last satisfactory inspection • variation application form clearly outlines present and proposed manufacturer [6]
USA	CBE 30, 30 days TELL, WAIT AND DO	• satisfactory cGMP inspection	• demonstration of equivalence → maintenance of quality characteristics: conformance to specifications by batch results[1] • Stability Guidance[2]: Commitment to place the first production batches and annual batches thereafter on long-term stability using the approved stability protocol of the application. The stability data have to be reported in the AR

[1]*Changes to an approved NDA or ANDA; SUPAC guidances do not cover this change, but are applicable to the manufacturing transfers of the specific dosage form;* [2]*Stability testing of Drug Substance and Drug Product-Draft Guidance* [52]

A transfer of the primary packaging site for a solid oral dosage form is classified differently in the EU and the US. In the EU a packaging transfer is generally not considered to have any impact on quality, safety and efficacy for an immediate release solid oral dosage form. By contrast, in the US this change is regarded as a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity or potency of the drug product. As both regions classify this change differently, the documentation requirements differ for these regions. Hence, two different documentation packages have to be prepared, which is a regulatory burden to companies that need to file the same variation in both regions. The variation

package for the EU is suitable for a "tell and do" notification. For the US, documentation has to be provided to demonstrate the equivalence to the previous site. Besides, a commitment to perform stability studies has to be provided. To perform stability studies is not considered as a documentation requirement for filing this change in the EU. Multinationally operating companies have to prepare these studies, which should be included in common data repositories for the international filing of changes, because there are further countries (e.g. South Africa), which also require these data.

In addition to the listed documents in the table, the suggested documentation package for the US to be provided by the applicant should include a copy of proof of GMP compliance of the new site and the updated sections of the dossier concerning the packaging part. The documentation package should be discussed with the FDA prior to submission. The time lines for meetings with the FDA and the planned submission of the change should be distributed within the company, so that a coordinated planning of the preparation for submission of the variation in the EU and the US can take place. The presumed transfer date should then be communicated to the logistics department.

Replacement or addition of a manufacturing site for all other manufacturing operations except primary and secondary packaging and batch release

Table 7 Comparison of EU and US requirements for replacement or addition of manufacturing site for all other manufacturing operations

Country	Change classification / approval time	Conditions	Documentation to be prepared by the MAH
EU	IB, 30 days TELL, WAIT AND DO	• Satisfactory inspection in the last 3 years • site is appropriately authorised • product concerned is not a sterile and/or biological product • validation scheme available or validation has been successfully carried out with at least 3 production scale batches [2]	• copy of current manufacturing authorisations (if site is in the EEA) • date and scope of the last satisfactory inspection • variation application form should clearly outline the present and the proposed manufacturer • batch numbers of batches used in the validation study should be indicated or validation protocol to be submitted • copy of approved release and end-of shelf-life specifications • batch analysis data on one production scale and 2 pilot scale batches (or two production batches) [6]
USA	CBE 30, 30 days TELL, WAIT AND DO	• satisfactory cGMP inspection • according to SUPAC-IR regarded as level 3 change, because the change is a transfer to a different campus	**According to SUPAC-IR** [46]: • location of the new site and updated batch records for regulatory filing • application and compendial release requirements • stability: one or three batches with three months accelerated stability data are reported in supplement, up to one

Country	Change classification / approval time	Conditions	Documentation to be prepared by the MAH
			or three batches on long-term stability data reported in AR (the less number of batches is required if a significant body of data is available- after 5 years for NCEs; 3 years for new dosage forms) • dissolution profile: dissolution profile at current and proposed site should be similar. • Further information as determined by FDA to make a proof on equivalence: validation data, batch analysis data

(continuation of the table from previous page)

The time lines to implement a site transfer, e.g. for the bulk tablet production, are the same in the US and the EU. This is an advantage, because a common date can be fixed for the manufacturing transfer to the new plant.

However, a difference exists in the supporting documentation that has to be submitted for the change. While the EU variation system requires relatively few supporting documents, in line with the concept of a notification, (e.g. batch numbers of validation batches instead of validation data), in the US, the applicant has to provide "raw data" to allow the FDA to evaluate the change. The FDA follows the so-called "bottom-up" approach for its assessment, i.e. the FDA re-analyses the raw data provided by the applicant. The notification procedure of the EU, matches to the "top-down" approach, i.e. the competent authorities trust in responsibility of the applicant to interpret their documentation to support the change. A closer check on the documentation will be done during the biannual inspection by supervisory authorities.

In order to prove equivalence between the manufacturing process at the old site and the manufacturing process at the new site, according to the SUPAC guidance, data on stability and dissolution have to be provided by the applicant. This is not a requirement in the EU for filing this variation, but these data have to be prepared by a multinationally working company for the international filing of variations.

The submission to the authorities in the US is dependent on the availability of 3 months accelerated stability data. Besides all pre-submission activities, this has to be taken into consideration by companies for the planning and coordination of the variation on a multinational basis. This additional requirement in the US represents a regulatory burden and a disadvantage with regard to the multinational filing of variations.

If the site change involves an equipment change or a manufacturing process change, then this should be considered as multiple related changes (*Changes to an Approved NDA or ANDA* [42]).

For multiple related changes where the recommended reporting categories for the individual changes differ, the FDA (CDER) recommends that the submission will be in accordance with the most restrictive of the categories recommended for the individual changes. In the EU each change has to be filed separately. The changes can be filed simultaneously, but cannot be grouped together in a single variation. In this case, the US system is more advantageous to industry.

The guidance for industry *SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms-Manufacturing Equipment Addendum* [49] differentiates classes (operating principles) and subclasses (design characteristics) of equipment. Equipment within the same class or subclass would be considered to have the same design and operating principle respectively. A change of equipment within the same subclass (e.g. different manufacturer) generally would not represent a change in operating principle and is considered to be the same under SUPAC-IR or SUPAC-MR. If the new site uses equipment of a different class as compared to the equipment of the previous site, this is considered as a change in design and operating principle. This equipment change has to be filed with the FDA. Equivalence has to be proven and a validation study that also covers the equipment qualification should be performed. In the EU, a change in the manufacturing equipment has to be filed as well, if there is a change to the operating principle. If documents in the dossier state the exact type and manufacturer of the equipment used and that is to be changed to the same equipment type of a different manufacturer, then this would also cause a variation in the EU even if the design and operating principle are the same. This is due to formal reasons and not based on a scientific explanation, because any amendment to the dossier has to be notified to the authorities as a variation.

6.3 Comparison of manufacturing changes between EU and US

Minor change in the manufacturing process of the active substance

Changes in the manufacturing process of an active substance require an evaluation by the authorities according to the EU variation system and the US system for post-approval changes.

Two major criteria are important for the assessment process in the US [51]:

- Equivalence of impurity profiles

The impact of the change is evaluated by determining the levels of existing and new impurities and the levels of residual solvents and inorganic substances.

- Equivalence of physical properties

Generally, only two physical properties of the drug substance, morphic form and particle size, are considered critical for evaluation of equivalence.

If equivalence cannot be demonstrated applicants should submit a PAS.

This approach is similar to the conditions in the EU to classify variations of manufacturing changes of the active substance. To file a change to the manufacturing process of the active substance as a minor change of type IB, the qualitative and quantitative impurity profile and the physicochemical properties have to remain unchanged. Furthermore, for active substances of non-biological origin, the synthetic route has to remain the same [2]. If this condition cannot be fulfilled, a major variation of type II has to be filed.

To correctly classify a change, the US system additionally takes into account the step of the manufacturing process in which the change occurs. This is based on the following considerations: The manufacturing process of the active substance is a sequence of reactions and purification steps. The isolation of the crude active substance and the subsequent purification steps in the manufacturing process have to comply with a state-of-the art pharmaceutical production. The impurity profile of the active substance is determined by the last chemical reaction step and the subsequent purification step, provided that the final intermediate is described by a specified impurity profile. This fact is considered by GMP regulations for active ingredients. The GMP requirements increase steadily up to the final intermediate and to the active substance [53]. In the US, this fact of the active substance synthesis is reflected in the system of handling post-approval changes to APIs.

The guidance for industry C*hange to an Approved NDA or ANDA* [42] indicates that any process change occurring after the processing step leading to the final intermediate in drug substance manufacture should be filed as a PAS. Any other change in the process or in process parameters for drug substance manufacture that do not fall under the scope of a PAS, i.e. all changes made in the process prior to the final intermediate are managed as a CBE 30 change or are even to be filed in the Annual Report.

The EU variation system [2][3] does not consider in which step of the manufacturing process of the active substance a change takes place and as a consequence all changes complying with the conditions are filed as type IB notifications or if they do not comply with the conditions, they have to be filed as a type II variation.

The BACPAC I [51] covers all changes in the manufacture of the active substance covering the initial synthesis steps and all subsequent steps up to the final intermediate, for example:

Changes in unit operations (e.g. addition, deletion, change in order, repetition of an existing unit operation on a routine basis), operating conditions (e.g. temperature, pH, reagent

stoichiometry, time). Addition or deletion of raw materials (e.g. solvents, reagents) or ancillary materials (e.g. resins, processing aids). Change in solvent composition (other than for analytical procedures). The following tables state the comparison between the EU and the US regarding changes in manufacturing process of an active substance.

Table 8: minor change in the manufacturing process of an active substance-EU approach

Country	Change classification / approval time	Conditions	Documentation to be prepared by MAH
EU	IB, 30 days	• No change in qualitative and quantitative impurity profile or in physicochemical properties • the active substance is not a biological substance • synthetic route remains the same [2]	• Amendment to the relevant sections of Part IIC or equivalent in the CTD format and of the approved DMF including a direct comparison of the present and the new process • batch analysis data (in comparative tabular format) of at least two batches (minimum) pilot scale manufactured according to the currently approved and proposed process • copy of approved specifications of the active substance [6]

Table 9: Changes in the manufacturing process of an active substance- US approach

Country	Change classification / approval time	Conditions	Documentation to be prepared by MAH
USA	AR 0 days	If equivalence is demonstrated prior to the final intermediate	• Description of change[1] • Specifications for new reagents and solvents, CoA of supplier, if appliable[1] • Evaluation of impurity profile and physical properties on three consecutive batches made by using material produced by the changed process, historical data for comparison[1]
USA	CBE, implementation upon submission	If equivalence is demonstrated at the final intermediate or drug substance	See above

[1] *BACPAC I*

These examples show that the post-approval guidance on CMC changes in the US is more detailed and scientifically based as compared to the current EU Regulations. Based on a detailed scientific and rational evaluation, it is possible in the US to classify minor changes as annually reportable. The US follow the same approach in differentiation between changes to an analytical procedure for the starting materials or for intermediates prior to the final intermediate which provide less risks of adverse effects on identity, strength, quality, purity or potency of a drug product and which are to be filed in the Annual Report and changes to an analytical procedure for the final intermediate and the final active substance which provide more risks of adverse effects on identity, strength, quality, purity or potency of a drug product and which are filed as a CBE (*Change to an Approved NDA or ANDA* [42]).

A similar scientifically based approach would be much appreciated by industry for the European Union, because every change can be considered according to its impact on quality, safety and efficacy of the drug substance and a lot of changes in a manufacturing process of a drug substance could even be filed as a type IA notification. EFPIA [25] made this suggestion, when the drafts of the Commission Regulations were reviewed (see table 2 in the Appendix). Unfortunately this approach has not been considered in the final Commission Regulations. This is a disadvantage when filing variations in the enlarged EU and when filing variations multinationally. A harmonised approach would reduce the regulatory and logistic burden and the changes could be implemented at the same time in the EU and the USA.

6.4 Comparison of the European variation system to the procedures for variations in Japan

6.4.1 Principles of changes to a medicinal product in Japan.

The drug approval system operating in Japan varies in many ways from the ones in the EU and the US. Therefore, the change system is completely different for the time being.

In Japan, a *Drug Manufacturing and Import Approval* and a *Manufacturing and Import Licence* is needed to market a medicinal product. A *Drug Manufacturing and Import Approval* is a governmental permission for a drug to be manufactured or imported, generally distributed and used for healthcare in Japan. For this purpose the Ministry of Health Labour and Welfare (MHLW) reviews the name, ingredients, composition, dosage, administration and adverse drug reactions of any drug before giving approval. This approval system is the essential basis for ensuring a good quality, safety and efficacy of medicinal products, which is the principal objective of the Japanese Pharmaceutical Affairs Law (PAL) [54].

A *Manufacturing and Import Licence* is issued after ensuring that the applicant is able to manufacture or import and to distribute the approved drug. This means that the manufacturing or business facilities of the applicant have sufficient structure and equipment, manufacturing

and quality control systems and human resources to deal properly with the approved drugs. In order to manufacture or import and to distribute drugs, manufacturers or importers must obtain a drug manufacturing or import licence for each of their manufacturing plants or business facilities from the Prefectural Governor (*manufacturing business licence*) and a manufacturing licence *(product manufacturing licence)* or import licence for each product from the MHLW.

If an approval of a drug has not been obtained, no manufacturing or import licence for the product is granted.

The legal basis for changes in both *Manufacturing and Import Approval* and *Licence* are stipulated in the Japanese Pharmaceutical Affaires Law (PAL) [54], as the holder of an approval is eligible to apply for partial changes in approved items in the approval as described in Article 14, Paragraph 7 of PAL [54], and for changes in the licence as described in Article 18 of PAL [54].

Changes may be related to the *Manufacturing and Import Approval* of a medicinal product or to the *Manufacturing and Import Licence*, or both. Depending on the category of the medicinal product, the application for approval of the changes has to be submitted to the MHLW or to the respective Prefectural Governor. This approach is quite different from the variation system in the EU and also from the US system. In these regions all variations, including those dealing with the manufacturing plants or business facilities, are directly addressed to the regulatory authority and not to the supervisory authorities. In both, the EU and the US, the regulatory authorities can be supported by the supervisory authorities in doing the evaluation of a change.

In Japan, the applications for variations, changes and amendments are generally filed at the time when the MAH applies for re-examination of the approval (laid down to 4 to 10 years by the MHLW) or for renewal of the licences after a period of 3 years. However, the application for variations, changes and amendments can be made at any time during the granted period.

6.4.2 Classification of changes and supporting documents

The Japanese system for post-approval changes differentiates between partial changes in approved items in drug manufacturing approvals ("partial changes") (Article 14, Paragraph 7 of the PAL [54]) and changes that require a new approval (Article 14, Paragraph 1 of PAL [54]), when the contents of a drug that has already been approved for manufacture are changed.

In principle, new approval applications are required for changes in the brand name, the active ingredients or their quantities, dosage forms, new indications, different patient or age

groups. Such modifications are considered as significant. Therefore, the applicant should consider filing an application for an entirely new *Manufacturing and Import Approval*.

Partial changes are changes that do not involve pharmacological changes to the product or marked changes in its appearance.

Partial change applications apply to changes to the quality and quantity of ingredients for other than active ingredients, posology, administration, indications and effects or to specifications and test methods. Partial change applications are also possible for changes in the manufacturing method, storage conditions and expiration date.

Changes to the drugs listed in the Japanese Pharmacopoeia are basically handled in the same way as those not included in the Japanese Pharmacopoeia.

The procedure of the change can be initiated by the holder of the Manufacturing or Import Approval or ordered by the MHLW as stipulated in the PAL (Article 74-2) [54].

A notification to the licence is necessary when a manufacturer closes down his plant, suspends operations of his plant, resumes previously suspended operations, or when he appoints a different supervisor for drug manufacture or specifies other matters as specified by the MHLW ordinance.

All partial changes of a *Manufacturing and Import Approval* and notifications to the licence should be notified to the authorities by using designated application forms.

In contrast to the EU, it is not possible to file variations in parallel. As long as an application for a partial change is pending, as a rule other partial change applications cannot be filed. Further applications for a partial change should be submitted only after approval of the previous partial change or after withdrawal of the previous partial change application. Interestingly, when new indications are added or for changes that result from reevaluations, partial change applications can be filed, even if other partial change applications are still under review. A consultation should be arranged with the authority about this issue.

The assessment of a change in Japan takes about one year [55]. Therefore, partial changes can be considered as "tell and wait" changes, but the time for approval is much longer as compared to that for a type II variation in the EU or a PAS in the US. In Japan, there is no separate classification and time line for minor changes ("tell and do" resp. "do and tell") as it is the case in the EU and the US.

For the data that needs to be submitted to support partial changes, applicants should consider the recommendations of the guidance *Drug Approval and Licensing Procedures in Japan, 2001* [56]. The data requirements differ for new approval applications as opposed to partial change applications. The requirements for partial change applications are structured according to defined columns: The ingredients and quantities column, manufacturing method column, specifications and testing methods column, storage condition and shelf-life column.

The requirements for any given change are not described in detail and have to be determined together with the authorities. The Japanese affiliate of a multinationally operating company should keep close contact with the authority in order to give advice on the supporting documents needed to file a change.

6.4.3 Comparison of the requirements for the addition of a manufacturing site between EU, USA and Japan

Cases involving the addition of a manufacturing plant to produce a medicinal product (e.g. the dosage form), which has been previously imported to Japan, require for a partial change approval in Japan. The time for approval takes approximately one year. The submission of data on bioequivalence is not necessary for drugs with the same formulation or manufacturing process that has been previously authorised. To demonstrate that, a document certifying that the manufacturer obtains all data and information concerning bioequivalence from the additional manufacturing site should be issued after the partial change approval application has been submitted to the authorities. For stability, a relative comparative test up to the time of approval is acceptable. Data on stability are not required, but it must be confirmed by relative comparisons that there is no loss of quality of the product due to the changes concerned until approval of the change. Therefore, the applicant has about one year to submit these data [56].

Compared to the EU variation system and the US system for post-approval changes, filing an additional manufacturing site takes the most time in Japan. For a globally operating company, having a medicinal product in the three regions on the market that is produced in one single plant, but should be transferred to a different manufacturing site, this means that the change cannot be implemented at the same time for all regions.

The EU variation system handles this change as a minor variation of type IB, provided that the conditions of Annex I are fulfilled [2]. Even if there is an additional change taking place in parallel with the manufacturing transfer (e.g. minor change in the manufacturing process, notification type IB), this change can be filed at the same time in parallel and an overall period of 30 days applies for approval of the change, provided that there are no grounds [2]. In the US this change requires a CBE 30 and the manufacturing transfer can take place 30 days after submission of the CBE 30 to the FDA [42] [46].

A multinationally operating company should transfer the production for the EU and the US markets simultaneously whereas the production transfer for the Japanese market could only take place at a later time point after the approval has been obtained.

This example demonstrates that the EU variation system provides a practical and efficient system for manufacturing transfers and therefore greatly facilitates the company's plant network strategy. The Japanese variation system is disadvantageous with regard to manufacturing transfers and causes logistic burden to companies.

6.4.4 Comparison between EU, USA and Japan: Replacement of animal-derived magnesium stearate by plant-derived magnesium stearate

In order to avoid the risk of TSE, companies are advised to replace the bovine magnesium stearate by magnesia stearate from vegetable origin.

In Japan, this change is not relevant for registration. In the chapter *Approvals for Partial Change Applications in Approved Items* of the guidance *Drug Approval and Licensing Procedures in Japan, 2001* [56] it is stated that partial change applications are not required for any changes in specifications that do not represent standards for assessing suitability of the description in the specifications and test methods. A change from animal-derived raw material to vegetable raw material is included in these considerations. Therefore, the change can be implemented immediately.

In the EU, this change is filed as a notification of type IA (change no. 23 b) of CR 1084/2003 [2] and 1085/2003 [3]) provided that the excipient magnesium stearate is not used in the manufacture of a biological product. The change can be implemented after the acknowledgement of a valid notification is received after 14 days. In the US, this change is to be included in the Annual Report and can therefore be implemented immediately [57].

From industry's point of view, this approach is much appreciated as it ensures a fast exchange of the animal-derived magnesium stearate by magnesium stearate of vegetable origin in the three main industrial areas. In the manufacturing facility, this change can be implemented almost at the same time, which avoids logistic burden. The implementation date should be coordinated taking into account the completion of the equivalence study demonstrating the impact of the change on the production of the final material required for the EU and the US and the submission of the notification considering the expected acknowledgement date in the EU.

6.5 Amendment of the Pharmaceutical Affairs Law and revision of the Japanese system for post-approval changes

The amendment of the Pharmaceutical Affaires Law (PAL) [54] was promulgated on July 31, 2002. It entails a major reform of the pharmaceutical industry responding to technological progress and diversifying economic activity in the 21st century. The revised PAL will enter into force on March 2005 [58] [59].

The revision of the PAL also has an impact on the system for handling post-approval changes in Japan.

Under the former PAL, two licences (*manufacturing business licence* and *product manufacturing licence*) and one manufacturing approval were required for a drug to be approved and its manufacture to be initiated. The latest revision has split the old manufacturing busi-

ness licence into a *manufacturing/marketing business licence* and a *manufacturing business licence*.

A company holding a *manufacturing/marketing business licence* has obtained a manufacturing approval for the drug and bears full responsibility for its efficacy, safety and quality. It can out-source drug production to a company holding the new *manufacturing business licence*. The manufacture must follow GMP. In addition, the drug *manufacturing approval* and *product manufacturing licence* have been unified in a *drug manufacturing/marketing approval* and the previous *product manufacturing licence* system has been abolished (abolish of Article 18 of PAL [54]).

The new rules have thus created a shift from a system focused on manufacturing to one similar to the systems operating in the EU and the US, which are centred on marketing with special emphasis on post-marketing measures. According to the new Japanese system, R&D-oriented companies no longer have to own production facilities. This leads to a more flexible operation for these companies.

According to the new Japanese PAL, any change to the details of the *manufacturing/marketing approval* will require a variation application. However, the abolition of the *product manufacturing licence* will increase the number of items requiring variation approval. In particular, manufacturing processes previously guaranteed by the *product manufacturing licence* will become items for variation approval. This mainly holds true for CMC changes made in production.

If the investigation or review of each variation takes as long as one year, this would have a negative impact on production. Therefore, the decision has been taken to introduce a system of notifications of minor changes, as it is already practised in Europe and the USA, which will apply to variations.

With the exception of changes that would have a major impact on quality, safety and efficacy, such as new indications and changes to the posology, the European and US systems will be referred to when considering what kinds of changes can be classified as "minor" [59].

Changes can be implemented immediately on submission of the notification and it is expected that this should enable simultaneous implementation of minor changes in Japan, Europe and the USA for products manufactured outside Japan. For a multinationally operating company, this approach will be much appreciated to reduce the administrative burden when filing variations internationally.

7 Conclusion and Outlook

Regarding the industrial practice, the new Variation Regulations provide simplified procedures to perform a variation, which are suitable to cope with an increased number of variations and more MS participating in a variation procedure in the enlarged EU. Especially for chemical-pharmaceutical changes that occur in a manufacturing facility, the implementation of a change represents less logistic burden, offers more economical benefits and even major changes can now be implemented in all concerned MS of the enlarged EU at the same time. The classification as a type II variation of all changes to or addition of a therapeutic indication of a medicinal product means a significant reduction regarding the time line for implementation. Still having the possibility to file a new application to add a new indication increases business flexibility. The new procedure for type II variations is more flexible as it allows different time lines to be set depending on the change and the urgency of the matter. The expedited procedure, possible for type II changes related to safety issues, as well as the harmonised implementation of these changes are of importance to protect public health in the enlarged EU. The MAH is responsible for the implementation and should treat this task with carefulness in order to avoid any harm to patients for which the MAH could be liable. The same applies to the USR to be implemented within an agreed time frame. The time line of 15 days seems quite short to prepare a documentation for the corresponding type II variation. For extensions, national and mutual recognition procedures are possible if the original authorisations are national. The MAH can choose to include the extension of a nationally authorised product into a MRP, which increases regulatory flexibility.

From industry's point of view, the target to reduce the workload in managing variations has not quite been achieved. In some cases, there are even increased requirements regarding the documentation. This is time-consuming and increases the costs of changes. The classification of changes is in many cases too restrictive and schematic. It does not offer any possibilities for a scientifically based consideration of an individual change, supported consequently by an appropriate documentation.

Although the allocation of the MRP variation number is now in the hands of the applicant and a documentation in English language is accepted in all EU countries, the submission principles and national peculiarities still represent an immense workload for industry when performing variations in the enlarged EU. Therefore, companies need an internal system to coordinate submissions and to follow-up on the variations.

Annex I and the corresponding *Guideline on Dossier Requirement for a type IA and IB Notification* still provide inconsistencies and need more definitions in order to avoid misinterpretations. Although it represents an immense workload, companies should reformat the quality

part of the dossier into the CTD format with all necessary information in order to maintain a proper documentation suitable for filing further variations.

With regard to the multinational procedure in performing variations, the new Variation Regulations offer clear improvements for the industrial practice. Type IA notifications provide only a minimal time line difference regarding the implementation of a change as compared to a change that can be implemented immediately and that is to be filed in the Annual Report or as a CBE in the USA. The time line of a notification of type IB corresponds to a CBE 30 in the USA. In the near future, Japan will introduce a system of minor changes as it is already practiced in Europe and the USA. A common approach in performing minor changes in the three main industry regions is aspired. This would mean less time line differences and a decreased logistic burden to industry in the future. It is a first step towards harmonisation. But currently, the classification of a change does not always lead to a change reporting category with similar time lines in the USA and the EU. The USA classify changes more scientifically based, has more differentiated reporting categories and in many cases there is a different approach in the assessment of a change regarding its impact on quality, safety and efficacy. For the time being, Japan assesses the changes completely differently from the USA and the EU. As a consequence there is still a variety of data requirements in the three main regions. Some of the differences result from different requirements for the registration dossier. Industry still has to cope with region-specific requirements, which is a clear regulatory burden.

Compared to the US and Japan, the addition of an indication can be implemented with the shortest time frame in Europe. For a globally operating company, this offers opportunities to launch a new indication of a product line firstly in Europe. This strengthens the European market.

Nevertheless, the variation system should be optimised in the future. The procedure for type IA notifications could be improved by an implicit acknowledgement. Likewise, the time line for the type IB notification procedure could be reduced. For the initiation phase, the pre-submission phase and the 24-hour procedure of the USR procedure, stricter time lines should be defined, especially when the PVWP needs to be consulted. The classification of changes should be reconsidered. In the future, it is expected that electronic submissions will facilitate the procedure, but it should be aimed at a harmonisation of national peculiarities and fees.

According to Directive 2004/27 amending Directive 2001/83 [19] and to Council Regulation 726/2004 [60] it is not mandatory anymore to establish a notification system or an administration procedure concerning minor variations and to define the concept of a minor variation. There could have been a better coordination between this fundamental change of legislation and the revision of the Variation Regulations. But the legislative texts of 2004 offer an opportunity for improvements of the variation system and open the EU for a further harmonisation in performing multinational variations.

8 Summary

The final versions of the Commission Regulations 1084/2003 and 1085/2003 entered into force on 17 July 2003 and applied from 1 October 2003. Especially industry requires a streamlined variation system in order to cope with the increased workload in performing variations and to facilitate the implementation of changes in the enlarged EU. This Master-Thesis discusses the impact of the new European Variation Regulations on the industrial practice of a multinationally operating pharmaceutical company and highlights the advantages and disadvantages in performing variations according to these Regulations in the enlarged EU and their suitability regarding the multinational procedure in performing variations with focus on a comparison of the three industry regions EU, USA and Japan.

The classification and procedures for minor changes of type IA and IB and the impact on industrial practice are examined by looking at administrative changes, manufacturing changes and changes affecting the quality control of the active substance and the medicinal product. For chemical-pharmaceutical changes, that occur in a manufacturing facility, the implementation of a change represents less logistic burden. It is an economic benefit, that the variation system offers the opportunity that production batches, manufactured to generate data to support the change, can be sold with the almost entire assigned shelf-life.

Major chemical-pharmaceutical changes can be implemented in a manufacturing facility for all concerned Member States of the enlarged EU at the same time. The classification as a type II variation of all changes to or addition of a therapeutic indication of a medicinal product means a significant reduction regarding the time line for implementation. Still having the possibility to file a new application to add a new indication allows for marketing options and increases business flexibility. The new procedure for type II variations is more flexible as it allows different time lines to be set depending on the change and the urgency of the matter. The expedited procedure, possible for type II changes related to safety issues, as well as the harmonised implementation of these changes are of importance to protect public health in the enlarged EU. The marketing authorisation holder is responsible for the implementation and should treat this task with carefulness in order to avoid any harm to patients for which the marketing authorisation holder could be liable. The same applies for urgent safety restrictions to be implemented with an agreed time frame, although the time line of 15 days seems quite short to prepare a documentation for the corresponding type II variation. For extensions, national and mutual recognition procedures are possible if the original authorisations are national. The applicant can choose to include the extension of a nationally authorised product into a MRP, which increases regulatory flexibility.

The Master-Thesis provides examples of more increased requirements regarding the documentation to support a change. The classification of changes is in many cases too sche-

matic and restrictive. It does not offer any possibilities for a scientifically based consideration of a particular change, supported consequently by an appropriate documentation. The submission principles and national peculiarities still reflect an immense workload on industry, especially if more Member States of the enlarged EU participate in a variation procedure.

With regard to the multinational procedure in performing variations, the Master-Thesis compares time lines and data requirements of the revised EU variation system with the systems of post-approval changes in the USA and Japan. By means of a comparison of manufacturing transfers and changes in the manufacturing process of the active substance, it is concluded that the time line differences between the USA and the EU to implement a change are minimised. But the US classifies the changes more scientifically based, has more differentiated reporting categories and in many cases there is a different approach in the assessment of a change regarding its impact on quality, safety and efficacy of the medicinal product. For the time being, Japan assesses the changes completely differently from the USA and the EU. With the revision of the Japanese Pharmaceutical Affaires Law, Japan will introduce a system of minor changes as it is practiced in the EU and the USA. A common approach in performing minor changes in the three main industry regions is aspired, which will provide less time line differences and will mean less logistic burden to industry in future.

The Commission Regulations 1084/2003 and 1085/2003 provide simplified procedures to perform variations, but the target to reduce the workload in managing variations has not quite been achieved from industry's point of view. With regard to a multinational procedure in performing variations, the new Variation Regulations offer an improvement for the industrial practice. Nevertheless, the variation system should be optimised in the future and suggestions are made in the Master-Thesis. The revised legislative texts of 2004 offer an opportunity for improvements of the variation system and open the EU for a further harmonisation in performing multinational variations.

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Useful links

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10 Appendix

Appendix 1

Appendix 2

Impact on the industrial practice-Classification of changes and the supporting documentation

Appendix 1

Flow-charts of the type II procedure according to the MRFG Best Practice Guide for the handling of Variations *in the Mutual Recognition Procedure:* Type II variations

	Recommended reduced (30-day) procedure for type II variations
Day 0	Start of the procedure, RMS notifies the timetable to the CMS`s by CTS (EudraTrack) and to the MAH by email/fax.
Day 15	RMS circulates the PVAR to the CMS`s and to the MAH
Day 20	CMS`s send the possible comments on the PVAR to the RMS
Day 21	RMS sends the request for supplementary information to the MAH and the CMS`s, clock-stop
Clock off period	Should not be longer than 10 + 10 days (10 days for the applicant to provide the responses and 10 days for the RMS to prepare the FVAR)
Day 22	RMS circulates the FVAR to the CMS`s and to the MAH
Day 27	CMS`s send the possible comments on the FVAR to the RMS
Day 30	End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC to the CMS`s and the MAH
	60-day procedure for the type II variations
Day 0	Start of the procedure, RMS notifies the timetable to the CMS`s by CTS (EudraTrack) and to the MAH by email/fax.
Day 40	RMS circulates the PVAR to the CMS`s and to the MAH
Day 55	CMS`s send the possible comments on the PVAR to the RMS
Day 59	RMS sends the request for supplementary information to the MAH and the CMS`s, clock-stop
Clock off period	Should not be longer than 60 + 60 days (60 days for the applicant to provide the responses and 60 days for the RMS to prepare the FVAR)
Day 60	RMS circulates the FVAR to the CMS`s and to the MAH
Day 75	The possible break-out meeting
Day 85	CMS`s send the possible comments on the FVAR to the RMS
Day 90	End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC to the CMS`s and the MAH

90-day procedure for type II variations

Day 0	Start of the procedure, RMS notifies the timetable to the CMS`s by CTS (EudraTrack) and to the MAH by email/fax.
Day 70	RMS circulates the PVAR to the CMS`s and to the MAH
Day 85	CMS`s send the possible comments on the PVAR to the RMS
Day 89	RMS sends the request for supplementary information to the MAH and the CMS`s, clock-stop
Clock-off period	Should not be longer than 90 + 60 days (90 days for the applicant to provide the responses and 60 days for the RMS to prepare the FVAR)
Day 90	Re-start of the procedure. RMS circulates the FVAR to the CMS`s and to the MAH.
Day 105	The possible break-out meeting
Day 115	CMS`s send the possible comments on the FVAR to the RMS
Day 120	End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC to the CMS`s and the MAH

Appendix 2

Impact on the industrial practice-Classification of changes and the supporting documentation for filing variations

Table 1: Administrative changes

Change	Classi-fication	Impact on industrial practice
1. **Change in the name and/or address of the marketing authorisation holder**	**IA**	• Classified as "tell and do" change → change can be implemented in a shorter time compared to the former Regulations • According to the requirements of the former *Guideline on Dossier Requirements for type I Variations* from November 1999, a signed declaration from the company stating that the MAH remains the same legal entity was sufficient, now a formal document from an official body is required → increased requirement • "same legal entity": transfer of the MA from one company to another cannot be considered as a type IA notification → restrictive from industry point of view
2. **Change in the name of medicinal product**	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. • For CP: EMEA made already an acceptance check to the name of the medicinal product and issues the letter of acceptance before the variation is submitted. An evaluation of the name change is therefore not required anymore during the variation procedure and this change should be classified as type IA. • Name changes of CP products may increase with the EU enlargement. The system of Community Trademarks (CTMs) will be transposed into the new acceded MS of the EU, as will Community designs. To counter the difficulty of prior rights of existing trademarks in the new MS of EU, there are also provisions in the treaty stating that prior rights obtained in good faith in an accession country must be respected. Where there is a prior right in the accession country, the CTM will not be valid. Pharmaceutical companies have to consider the impact of any existing trademarks on these new markets. Some names of the medicinal products cannot be pronounced in the new MS or have a different meaning → a name change will be the consequence. This change is expected to increase and a quick handling would be appreciated (Type IA variation). • For MRP-products: an evaluation of the name change is necessary → type IB notification.

Change	Classi-fication	Impact on industrial practice
3. **Change in the name of the active sub-stance**	**IA**	• This change has not been filed as a variation in the former Regulations • In granting or amending the name, the WHO would have already carried out a review of the appropriate documentation → industry opinion: a simple letter should be required to inform the authorities.
4. **Change in the name and/or address of a manufacturer of the active substance where no European Pharmacopoeia certificate of suitability is available**	**IA**	• Classified as "tell and do" change → change can be implemented in a shorter time compared to the former Regulations • a formal document of the relevant official body is required, in which new name and/or address is stated. • With the EU enlargement, manufacturers of the active substance may be sold to multinationally operating companies extending their manufacturing facilities. Change in the name of the same manufacturing site will be possible. A quick handling of this change is appreciated.
5. **Change in the name and/or address of a manufacturer of the finished product**	**IA**	See change no. 4. It is also possible to provide the modified manufacturing license.
6. **Change in ATC Code**		
a) Medicinal products for human use	**IA**	• This change has not been filed as a variation in the former Regulations • Industry opinion: In granting or amending the ATC code, the WHO has already carried out a review of the appropriate documentation; a simple letter should therefore be required.
b) Veterinary medicinal products	**IA**	See change no. 6 a)

[2], [3], [4], [5], [6], [13], [15], [17], [25] [37], [38], [39]

Table 2: Changes in the manufacturing of the active substance and medicinal product

Change	Classi-fication	Impact on industrial practice
7. Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product		
a) Secondary Packaging	**IA**	• Classified as "tell and do" change → variation can be implemented in a shorter time compared to former Regulations • Company is dependent on the relevant inspection service being able to carry out the inspections in the relevant frequency for companies outside the EEA. If there are no resources the site transfer cannot be filed. It is uncertain if the accession countries can cope with all inspections according to European requirements. This would be a delay for multinationally operating companies to transfer this part of manufacturing process in order to gain capacity to supply the market.
b) Primary Packaging site		
1. Solid pharmaceutical forms	**IA**	• See comment change no. 7 a) • sterile and biological products are excluded and have to be filed as a type II variation→ more restrictive than the former Regulations.
2. Semi-solid or liquid pharmaceutical forms	**IB**	• Classified as " tell, wait and do" change. The filling process is more critical than the primary packaging of a solid form. Due to the reason that no product specific documentation (e.g. qualification of the filling process) has to be submitted, the demonstration that the change does not affect the quality, safety and efficacy of the product is based on the same (administrative) documentation as for the IA notification. → documents apply rather for a type IA notification than for a type IB notification. • Company is dependent on the relevant inspection service being able to carry out the inspections in the relevant frequency. → see comment change no. 7a) • Exclusion of sterile and biological products → see comment change no. 7b) no. 1

Change	Classi-fication	Impact on industrial practice
3. Liquid pharmaceutical forms (suspension, emulsion)	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. The filling process is more critical and needs an evaluation to demonstrate that quality, safety and efficacy are not affected. • Company is dependent on the relevant inspection service being able to carry out the inspections in the relevant frequency. → see comment change 7a) • Exclusion of sterile and biological products → see comment change no. 7b) no. 1 • Validation-Advantage: The Validation does not need to have been finished at the time of submission of the variation. The validation scheme according to CPMP/QWP/848/96 can be provided and validation work and filing the variation can be done in parallel→ this saves time, because mostly the analytical testing of the validation batches takes the most time. The validation of the manufacturing operation at the new site has to be successfully carried out prior to release the product to market. The validation batches can be commercialised in almost the assigned shelf-life. Regulatory authority will not assess validation data. • Validation-Disadvantage: In the former *Guideline on Dossier Requirements for Type I Variation,* it is not explicitly required to give information in validation (except biological product)→ It is now a requirement to check the state-of the-art practice in companies.
c.) All other manufacturing operations except batch release	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. These manufacturing operations are more critical and need an evaluation of the provided documentation to demonstrate that the quality, safety and efficacy are not affected. • Company is dependent on the relevant inspection service being able to carry out the inspections in the relevant frequency → see comment change no. 7a) • Exclusion of biological products → see comment change no. 7a) • Validation-Advantage: see comment of change no. 7 b) Nr. 3 • Validation-Disadvantage: see comment of change no. 7 b) Nr. 3
8. Change to batch release arrangements and quality control testing of the finished product		

Change	Classi-fication	Impact on industrial practice
a) Replacement or addition of a site where batch control/testing takes place	**IA**	• Classified as "tell and do" change → change can be implemented after the receipt of a valid notification (14 days). It allows a quick transfer to another testing site after the method transfer has been successfully completed → inclusion of new sites in the enlarged EU is facilitated. • Biological medicinal products are excluded, although they are covered by batch release at OMCL and companies QP release. For biological medicinal products this change has to be filed as a type II variation→ more restrictive than the former Regulations. Especially for immunologicals: Even if the same procedures and reference materials are used, methods are sometimes not easy to implement and the consistency of testing needs to be demonstrated by an appropriate validation. → evaluation is necessary, but a Type IB notification (evaluation by RMS) should be possible.
b) Replacement or addition of a manufacturer responsible for batch release		
1. Not including batch control/testing	**IA**	• Classified as "tell and do" change → change can be implemented after the receipt of a valid notification (14 days). It allows a quick transfer to another site after the method transfer has been successfully completed. → inclusion of new sites in the enlarged EU is easy possible.
2. Including batch control testing	**IA**	• See change no. 8a)
9. Deletion of any manufacturing site (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place)	**IA**	• Classified as "tell and do" change → change can be implemented in a shorter time than before. Industry decision to delete a site can be done easily from regulatory point of view. This causes more flexibility in the enlarged EU to organise the responsible sites.

Change	Classi-fication	Impact on industrial practice
10. **Minor change in the manufacturing process of the active substance**	IB	• Classified as "tell, wait and do" change. → time for the variation procedure is the same compared to the former Regulations. → too restrictive: all minor changes are considered as type IB notifications. Trivial changes should be classified as type IA notifications, where this does not affect the specification. Considered as type IA notifications are: Change in unit operations (e.g. addition, deletion, change in order, repetition of an unit operation on a routine basis) Minor change in operating conditions (e.g. temperature, change in mixing times) Minor changes for early synthetic steps (up to a final intermediate step) in the manufacture of the active should be subject to a type IA notification → little potential to impact the final active substance Only changes in the last step of the manufacturing process of the active substance should be type IB notifications. • Condition: no change in qualitative and quantitative impurity profile → restrictive; in the former Regulations no new impurities should be stated, but a change in impurity levels was possible as long as it is *below qualification limit.* Industry suggestion: The requirements regarding the condition: no change in qualitative and quantitative impurity profile or in physico-chemical properties should be clarified → Considering here the US-FDA`s approach in BACPAC guidance which uses equivalence of the quality of intermediates and/or active substances as a science based key criterion for classification of changes→ many changes could be classified as type IA notification requiring a reduced documentation → This would lead to a global harmonisation.
11. **Change in batch size of active substance or intermediate**		

Change	Classi-fication	Impact on industrial practice
a) Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation	**IA**	• Classified as "tell and do" change → variation can be implemented in a shorter time compared to the former Regulations. If production batches in the new batch sizes are available, the variation can be submitted and the batches released to market after receiving the acknowledgement of a valid notification after 14 days.→ batches can be commercialised with the assigned shelf-life. There are no losses for industry. The adaptation to market requirements of an enlarged EU is facilitated. • Industry suggestion: Batch size changes should only require a variation if the change adversely affects the identity, strength, quality, purity or potency of the active substance. The restriction "up to 10 fold" should be deleted → the FDA has decided that such batch size changes restrictions are unnecessary→ a harmonised approach is recommended. • Industry opinion: It is not clarified, if the change applies to the final step of a synthesis or to all steps described in the application. Industry suggests a threshold → a variation should not be needed if the change in batch size occurs prior to the final synthesis step and thereafter if the change does not exceed +/- 25 %. This corresponds to the experience of chemical production where the batch size has to be adapted to the amounts of intermediates.
b) Downscaling	**IA**	→ see comments change no. 11a) • Condition: the change is not an unexpected event during production or because of stability concerns → downscaling requires a robust process and it should be differentiated between unexpected events documented by deviation system and permanent post-approval changes documented by variation system.
c) More than 10-fold compared to the original batch size approved at the grant of marketing authorisation	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary. • Industry suggestion and industry opinion → see comment change no. 11 a) • Inconsistency between the condition test results of batches being available with the new batch size (2 batches) and batch data to be provided (at least 1 batch) in the documentation. The conditions require 2 batches to be available. The documentation requirements state that the next 2 production batches should be available upon request. For industry it would be an advantage to produce only 1 batch prior to submission of the variation.

Change	Classi-fication	Impact on industrial practice
14. **Change in the manufacturer of the active substance or starting material/reagent/intermediate in the manufacturing process of the active substance where no European Pharmacopoeia Certificate of Suitability is available**		• General: The change is extended to cover starting materials and reagents. The manufacturer of a reagent does not have to be stated in a dossier. The guideline CPMP/QWP/130/96 Note for Guidance on Chemistry of the new active substance states that only the name and address of the starting material supplier should be provided. If an intermediate is purchased in addition by an external supplier, it becomes a starting material as well and the manufacturer has to be filed.
a) Change in site of already approved manufacturer	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary. • Industry comment: Neither the European Drug Master File Procedure, nor the Notice to Applicants require the indication of suppliers of intermediates and reagents or starting materials. These terms would only be registered in exceptional circumstances. If this information has been registered, it should be a type IA notification, because the change occurs prior to the final step of the active substance process. It presents a lower risk than changes to the active substance, itself. The change should only occur to the final intermediate → a more harmonised approach with the FDA would be appreciated.
b) New manufacturer (replacement or addition)	**IB**	See comment change no. 14 a) • It is a condition that the manufacturer does not use a drug master file (DMF). These changes are filed as type II variations → industry will avoid switching to manufacturers with EDMF documentation in order to avoid long variation procedures. Companies will prefer manufacturers with CEPs.
18. **Replacement of an excipient with a comparable excipient**	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary. • As a condition in the former Variation Regulations it is stated that there is no change in the dissolution profile, now it is stated as a condition that the dissolution profile is comparable to the old one. → This is a more technical realistic condition. For solid dosage forms, comparative dissolution profile data of at least 2 pilot scale batches of the finished product in the new and old composition is required. In the former *Guideline on Dossier Requirements of Type I variations* data of at least one pilot/production batch of the finished product in the new and the old composition is required → increased requirements. • The exchange of an excipient with a comparable excipient for a medicinal product containing a biological active substance is excluded now → more restrictive compared to former requirements

Change	Classi-fication	Impact on industrial practice
23. **Change in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material**		• The change is newly introduced to the Variation Regulations due to the experience of the last years where companies have replaced BSE risk materials by materials of vegetable origin (e.g. magnesia stearate of bovine origin by magnesia stearate of vegetable origin).
a) Excipient or reagent used in manufacture of biological active substance or manufacture of a finished product containing biological active substance	**IB**	• Classified as "tell, wait and do" change -> an evaluation by the RMS/Rapporteur is needed, because of the complexity and particulars in the manufacture of biological medicinal products. • Industry opinion: If the excipient and finished product release and end-of-shelf-life specification remain the same (stated as a condition), it should not be required to provide a study of equivalence.
b) Other cases	**IA**	• Classified as a "tell and do" change → quick implementation of bovine-free excipients are possible. One batch in production scale will be manufactured to qualify the vegetable or synthetic excipient. Due to the quick procedure the batch can be released to market in almost the assigned shelf-life → industry is encouraged to switch the source of excipient.
24. **Change in synthesis or recovery of a non-pharmacopoeial excipients (when described in the dossier)**	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary. • Biological products are excluded in the new Variation Regulations →change requires a type II variation • Stricter conditions regarding impurities: no change in qualitative and quantitative impurity profile. In the former Regulations the conditions stated no new impurity or change in level of impurity which, would require a further qualification in safety studies→ the synthesis/recovery follows stricter conditions. • Comparative dissolution profiles for finished product required, where appropriate or for herbals: disintegration time → increased requirements compared to former requirement.
28. **Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings and ampoules, change of needle shield (different plastic used))**	**IA**	• Change is newly introduced to the variation system. The colour of flip-off and OPC ampoules provide information for doctors and nurses. Regarding the danger on change by mistake and the impact on safety, it is appreciated to have this change included to the variation system now. Any change on that has to be documented and notified.

Change	Classi-fication	Impact on industrial practice
30. **Change (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the dossier); spacer devices for metered dose inhalers are excluded**		• Common practice in the writing of a CMC-part (Module 3) is not to state the supplier of the packaging material in detail. Filing the supplier as e.g. COMPANY, provides flexibility. As a consequence, a change in suppliers can take place without filing a variation. This is possible under the condition that the qualitative and quantitative composition of packaging components and sterilisation methods and conditions (if applicable) remain the same and specifications and control methods are equivalent.
a) Deletion of a supplier	**IA**	• This change follows a "tell and do"-notification, provided no packaging or device component is deleted and the CTD/part IIC section is amended properly.
b) Replacement or addition of a supplier	**IB**	• This change needs an evaluation in order to demonstrate that the quality is not affected. This has to be demonstrated by proof of CE marking and a comparable table of current and proposed specification and complying with the listed conditions (see change no. 30).
32. **Change in batch size of the finished product**		• Conditions of the change excludes retard tablets, sterile dosage forms and biological medicinal products→ changes in batch size for these products are filed as type II variation → more restrictive compared to the former Variation Regulations.
a) Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation	**IA**	• Classified as "tell and do" change → variation can be implemented in a shorter time compared to the former Regulations. Adaptation to market requirements is facilitated, if all documents are available. In an enlarged EU more MS will be included in a MRP-procedure and 25 MS are included in a CP and once the product can be supplied an increase in batch size a better market supply will be possible → advantage for industry. • To have the process validated with the new batch size is a state-of the-art requirement in industrial practice. It is stated as a condition for this variation now. • Validation-Advantage: see comment of change no. 7 b) no. 3 Validation-Disadvantage: see comment of change no. 7 b) no. 3
b) downscaling down to 10-fold	**IA**	• See comments of change no. 32 a) • Condition: the change is not an unexpected event during production or because of stability concerns See comment change no. 11 b).

Change	Classi-fication	Impact on industrial practice
c) Other situation	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary. • Regarding validation → see comment change no. 32 a) • It is a condition that the change in batch size is not a result of unexpected events or due to stability concerns → see comment change no. 11 b) • Stability studies have been started with at least one pilot scale or industrial scale batch and at least 3 months stability data are available → increased requirements, because in former Variation Regulations and *Guideline on Dossier Requirements of Type I variations* no stability data were required. Industry has to plan manufacturing batches where the manufacturing change has been implemented and the 3 months stability data have to be generated in advanced before the variation can be filed.
33. **Minor change in the manufacture of the finished product**	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to former Regulations. Evaluation by the RMS/Rapporteur is necessary → too restrictive: all minor changes are considered as type IB. Trivial changes should be classified as type IA, where this does not affect the specification: Considered as type IA: Change in order of components for liquid dosage forms, changes in order of solutions used in unit operations (e.g. at granulation process), minor changes (+/- 20 %) in mixing and blending time, temperature and or other process conditions. This would reflect the distinction made by Commission NTA working group on changes to analytical method. A definition of what is a minor and a major change in manufacturing process is necessary. Industry thoughts for a minor change: Not affecting a step in the manufacturing process identified to be critical to release, no change in technology and equipment, only affecting one step in process, no change in IPC limits. • Stability studies have been started with one pilot scale or industrial scale batch and at least 3 months stability data are available → increased requirement; see comment change no. 32 c) • Batch Analysis data have to be provided in comparative tabulated format on a minimum of one batch manufactured to both current and proposed process. Next 2 batches should be available → increased requirements. • It is stated precisely as a condition that in case of a change in sterilisation process, the change is to a standard pharmacopoeial cycle only → more precise requirement compared to previous Regulations.

Change	Classi-fication	Impact on industrial practice
34. **Change in colouring system or the flavouring system currently used in the *finished product***		• Industry concerns on stability requirements regarding changes in colouring/flavouring system. EFPIA suggestion: stability studies have been started at the time of submission and a declaration should be submitted indicating that at least 2 pilot scale or industrial scale batches would be available prior to making the change in factory. Industry opinion is that conducting of stability data is not necessary in every case (only if the colorant has the function of light protection). Mostly negative influences on stability occur during the first 6 to 9 months of a study, long-term studies over years do not seem appropriate for such modifications.
a) Reduction or deletion of one or more components of the		
1. colouring system	**IA**	• Classified as "tell and do" change → variation can be implemented in a shorter time compared to the former Regulations. • Exclusion of biological veterinary medicinal products for which <u>colouring</u> is important for the uptake by target animal species → extended necessary requirement • In classical production of coated tablets, the formulation is in principle completed before a very thin colouring coating is added in the last step. Reduction or deletion of a colouring agent using the same amount of coating does not change anything in the formulation relevant for stability.
2. flavouring system	**IA**	• Classified as "tell and do" change → variation can be implemented in a shorter time compared to former Regulations. • Exclusion of biological veterinary medicinal products for which <u>flavouring</u> is important for the uptake by target animal species → extended necessary requirement. • If there is no change in functional characteristics (e.g. essential oils having certain antimicrobial and thus stabilising properties), the reduction or deletion of the flavouring system leads to a reduction of complexity of the matrix of a formulation. Changes occur in the first 6 to 9 months if any, therefore a long-term stability study does not seem to be necessary.
b) Increase, addition or replacement of one or more components of		

Change	Classi-fication	Impact on industrial practice
1. colouring system	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to former Regulations. Evaluation by the RMS/Rapporteur is necessary. • Exclusion of biological veterinary medicinal products → see comment change no. 34a) no. 1 • TSE requirements (Ph. Eur. TSE-certificate available or assessed by competent authority according to the relevant Note for Guidance) are newly introduced.
2. flavouring system	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary. • Exclusion of biological veterinary medicinal products → see comment change no. 34 a) no.. 2) • TSE requirements→ see change no. 34 b) no. 1 • Data on consistency of composition is not required explicitly anymore, (e.g. GLC data of 3 batches)
35. ***Change in coating weight of tablets or change in weight of capsule shells***		
a) Immediate release oral pharmaceutical forms	**IA**	• Classified as "tell and do" change → variation can be implemented in a shorter time compared to the former Regulations. • Dissolution data on a minimum of 2 pilot scale batches are required → increased requirements, in the former *Guideline on Dossier Requirements for Type I variations* dissolution data on at least one batch was required. The dissolution profile of the new product should be comparable to the old one and stated a technical realistic condition in the new Variation Regulations. • Stability studies on at least 2 pilot batches or industrial scale batches with 3 months stability data are at the disposal of the applicant → increased requirements; in the former *Guideline on Dossier Requirements for Type I variations* stability was not required. MAH has to plan to manufacture batches with the new coating weight or capsule shell weight and calculate the time line as when the submission of the variation is possible. The costs for this change are increased.
b) Gastro-resistant, modified or prolonged release pharmaceutical forms	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same as compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary. • Requirements regarding dissolution and stability are increased → see comment change no. 35 a)

Change	Classi-fication	Impact on industrial practice
36. **Change in shape or dimensions of the container or closure**		
a) Sterile pharmaceutical forms and biological medicinal products	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary. • In case of change in the headspace or a change in the surface/volume ratio, stability studies have to be performed on 2 pilot scale batches at least. Batch numbers have to be indicated in the documentation. In the former Variation Regulations it was stated in the conditions that the stability of the product should be unchanged. Now, this requirement has to be put in concrete terms and has to be proved by stability studies. → Industry has to plan to package the product in the new container and to perform stability data and to submit the variation when three months stability data are available. • Industry view: For many pharmaceutical preparations it is not necessary to perform additional stability data when a smaller or bigger pack size for a finished product will be added. The necessity on conducting stability trials should be evaluated on a case-by-case basis. • Only samples of the new container/closure have to be provided to specific MS according to NTA Chapter 7. This applies mostly for the new acceded MS.
b) Other pharmaceutical forms	**IA**	• Classified as "tell and do" change → variation can be implemented in a shorter time compared to the former Regulations • Regarding stability and samples → see change no. 36 a)
39. **Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of ink used for product marking**	**IA**	• Classified as "tell and do" change → variation can be implemented in a shorter time compared to the former Regulations • The former Regulations stated the condition that the new marking do not cause any confusion with other tablets or capsules → this is not a requirement in the new Variation Regulations. • Declaration that the release and end-of-shelf-life specifications have not changed, except for appearance, is not required anymore as a supporting document → it is a condition now.
40. **Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative and quantitative composition and mean mass**		

Change	Classi-fication	Impact on industrial practice
a) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary. A down classification is only intended for immediate release pharmaceutical dosage forms. • Declaration that release and end-of shelf-life specifications have not been changed is not required anymore to be submitted with the variation → now, stated as a condition.
b) All other tablets, capsules, suppositories and pessaries	**IA**	• Classified as "tell and do" change → variation can be implemented in a shorter time compared to the former Regulations. The separation of gastro-resistant and modified release tablets and the immediate release solid dosage forms has advantages for industry • Comparative dissolution data are not required to be submitted in the documentation for immediate release dosage forms. The requirement that the dissolution profile of the reformulated product is comparable to the old one is stated as a condition. It is the applicant's responsibility to evaluate this. • Data on breakability are not required anymore to be performed for immediate release solid dosage forms. These are decreased requirements with regard to the documentation. • Regarding the Declaration for release and end-of-shelf-life specification → see change no. 40 a)
41. **Change in pack size of the finished product**		• Regarding stability, there are no mandatory prescriptions. Stability studies will only have to be conducted if stability parameters are affected. It is the applicant's responsibility to evaluate this. • A declaration that the container and closure composition is unchanged and in case of plastics an assurance that the polymer wall thickness is at least as thick as the current packs, is not required anymore→ it is stated now in the condition that the primary packaging material remains the same. • It is more convenient for industry to determine all pack sizes to be included in the authorisation procedure instead of introducing additional pack sizes after the MA has been granted. If the MAH wishes to introduce an additional pack size that is not included in the SmPC in one MS, after an MA has been granted, a MRP variation has to be triggered. If the pack sizes are already listed in the SmPC, it does not raise a MRP variation and the introduction of pack size is filed nationally.
a) Change in the number of units (e.g. tablets, ampoules, etc.) in a pack		

Change	Classi-fication	Impact on industrial practice
1. Change within the range of currently approved pack sizes	**IA**	• Classified as "tell and do" change → Change can be implemented in a shorter time compared to the former Regulations. A change in the number of units in a pack within the range of currently approved pack sizes is facilitated. The pack size is consistent with posology and treatment duration as approved in the SmPC.
2. Change outside the range of the currently approved pack sizes	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary and the MAH has to bring a justification for the new pack-size showing to be consistent with the dosage regimen and duration as approved in SmPC. • The RMS will involve the CMS in the evaluation of the change due to the reason that this change has an impact on reimbursement issues in the MS. The RMS needs an input from the CMS.
b) Change in fill weight/fill volumes of non-parenteral multi-dose products	**IB**	• See change no. 41a) no. 2
43. Addition or replacement or deletion of a measuring or administrative device not being an integrated part of the primary packaging (spacer, devices for metered dose inhalers are excluded)		• Change was not included in the Annex I of the former Variation Regulations and was classified as a type II variation. The change is classified in the new Variation Regulations as a minor change of the categories of type IA and type IB –> advantage for industry to make changes on administrative or measuring devices.
a) Medicinal Products for human use		
1. Addition or replacement	**IA**	• Classified as "tell and do" change → the variation can be implemented in a shorter time compared to the former Regulations. • No assessment is necessary, because the additional or replaced device has a CE marking and the notified body has already assessed the conformity with the relevant guidelines.
2. Deletion	**IB**	• Classified as "tell, wait and do" change → the variation needs an evaluation by CMS. It has to be assessed if the medicinal product can be accurately delivered without the measuring or administrative device.
b) Veterinary medicinal products	**IB**	• Classified as " tell, wait and do" change → the variation needs an evaluation. Veterinary medicinal products do not fall under the scope of a CE marking and therefore an evaluation is justified. Data to demonstrate accuracy, precision and compatibility have to be provided by the applicant that will be evaluated by the authorities.

[2], [3], [4], [5], [6], [13], [15], [17], [25] [37], [38], [39]

Impact on the industrial practice-Classification of changes and the supporting documentation for filing variations

Table 3: Changes affecting the quality control of the active substance and finished product

Change	Classi-fication	Impact on industrial practice
12. Change in the specification of an active substance or a starting material/ intermediate/reagent used in the manufacturing process of the active substance		• Change is extended to cover changes in specifications and testing methods for reagents. • Condition: the change is not an unexpected event arising during manufacture and it should be differentiated between unexpected events documented by deviation system and permanent changes documented by the variation system.
a) Tightening of specification limits	**IA or IB**	• Classified as "tell and do" change under the condition that the change is not a consequence of any commitment from previous assessments to review specification limits → change can be implemented in a shorter time compared to the former Regulations. • Classified as "tell, wait and do" change if the change is a consequence of a commitment from previous assessment. A type IB variation with an evaluation is a double of work. Industry fulfils commitments from an issue already assessed. Satisfactory completion of the commitment should only require a simple notification to the authorities as a type IA notification → It is disadvantageous to industry if a commitment can be implemented after a 30 days evaluation. Tightening of specification limits should be considered as type IA notification, no matter what the origin is, since this represents an improvement in quality. • For tightening of specifications of the active substance a comparative dissolution profile is not required anymore. →tightening of specifications requires less data than in former *Guideline on Dossier Requirements for type I variations*. Industry can based on experience in production tighten the specification in a short time.
b) Addition of a new test parameter to the specification of		

Change	Classi-fication	Impact on industrial practice
1. an active substance	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary. • Justification for not submitting a new bioequivalence study (if relevant) and comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification, is stated as requirement in the *Guideline on Dossier Requirement for Type IA and IB Notifications*. An addition of a new specification or testing procedure does not result in a new/changed product, nor implies it a change in the quality. Therefore there is no necessity to make dissolution profiles or to justify for not submitting a new bioequivalence study. A declaration that there is no impact on finished product dissolution parameters should be sufficient. Requirements are only relevant if the added specification concerns the physical properties of an active substance used in solid-oral dosage forms and even then these data are based on development data. • Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way→ Exclusion of the NIRS-method from minor variations. They have to follow a type II procedure. NIRS is a established and validated method and described in Ph. Eur.. If the requirements of the *CPMP/QWP Note for Guidance on the use of Near Infrared Spectroscopy by the Pharmaceutical Industry* are fulfilled and appropriate data are provided in the dossier, the introduction of this method should follow a type I B notification → regulatory burden would stop industry from introducing new, quick methods to the quality control area. • Definition of the term non-standard technique is needed. EFPIA suggestion: A standard technique is one in which the methodology is not described in a Pharmacopoeia.
2. a starting material/intermediate/ reagent used in the manufacturing process of the active substance	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary. • This variations and their condition cover aspects of different types of substances (reagents, intermediates, starting material) that have a very different status in the manufacture from a technically and from a GMP point of view. Therefore it is necessary that these different substance types should be dealt with different classification of variations with different conditions/requirements → a scientifically based approach would be appreciated from industry point of view. • Regarding exclusion of NIRS-method → see change 12 b) 1.

Change	Classi-fication	Impact on industrial practice
13. **Change in test procedure for active substance or starting material, intermediate or reagent used in the manufacturing process of the active substance**		• Change is extended to cover changes in test procedures for reagents. • Change excludes active substances, starting materials, intermediates or reagents of biological origin → These have to be filed as a type II variation. Industry opinion: if the test procedures are validated and specification limits are not affected, there should be no difference to a biological product and a type IB notification should be possible. In the former Variation Regulations and *Guideline on Dossier Requirements for Type I Variations* changes in test procedures for the active substance are filed as a type II variation only if the test procedure is not a physicochemical method.
a) Minor change in the approved test procedure	**IA**	• Classified as "tell and do" change → variation can be implemented in a shorter time compared to the former Regulations. • Conditions state precisely that the method remains the same, i.e. no change in chromatographic properties of the method and no new impurities should be detected, the method is equivalent to the former one. This is demonstrated by results of method validation. Regarding the impurities, the previous *Guideline on Dossier Requirements of type I variation* (November 1999) stated the possibility of new impurities. If the new impurity is detected with the new test procedure, a justification should be provided that the newly detected impurity is toxicologically acceptable. To file this change as a type IA notification according to the new Variation Regulations no new impurities should be detected. This would require an evaluation of the change by a type II variation. • A documentation is required in updating the CTD sections → advantageous to industry to file a small change in testing procedures with a notification. Revalidation studies stay in the responsibility of the applicant and might be controlled by supervisory authority during inspection. • No declaration has to be provided, that the specifications have not been changed.
b) Other changes to a test procedure, including replacement or addition	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to former Regulations. Evaluation by the RMS/Rapporteur is necessary. • Exclusion of the NIRS-method from minor variations → see comment change no. 12 b) no. 1 • The documentation should contain comparative validation results showing that the current test and the proposed test are equivalent. This has been stated as a condition and has to be proved by data.

Change	Classi-fication	Impact on industrial practice
15. Submission of a new or updated European Pharmacopoeia certificate of suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance		• This change is newly introduced as a separate change. Changes around a certificate of suitability (CEP) were included in several changes in the *Guideline on Dossier Requirements for Type I Variation* before (change nos. 11, 11a, 11 b, 12, 13, 14, 26, 34) → more structured compared to the former variation system • Industry opinion (EFPIA): Since all CEPs and its changes have already been technically reviewed and approved by EDQM assessors, many of whom are assessors within their national agencies, it is a double regulatory and administrative burden on industry and regulators to resubmit these change under the listed conditions as a variation. These changes should require a simple notification to authorities to introduce the new CEP to the documentation and not a variation procedure.
a) From a manufacturer currently approved	**IA**	• Classified as "tell and do" change → change can be implemented in a shorter time compared to the former Regulations. • Documentation No. 4, stating that the variation application should outline the present and proposed manufacturer, does not give useful information for an updated CEP from a manufacturer currently approved. Present and proposed manufacturers are the same. • Update of a CEP with changes in the additional (to European Pharmacopoeia) specifications for impurities, which can happen if manufacturing method changes, requires a type II variation (condition 2).
b) From a new manufacturer (replacement or addition)		• *Condition 2: <u>unchanged</u> additional (to European Pharmacopoeia) specifications for impurities and product specific requirements (e.g. particle size, polymorphic form).* If a CEP for an active ingredient has a limit of an impurity (residual solvent) listed in a CEP as an additional specification and the additional or replacing manufacturer of the active substance does not use this solvent in its manufacturing process and consequently the new CEP does not use this specification, but all other specifications are indeed identical, then this variation should be a type IA notification. According to the revised Variation Regulations, this change would be a type II change → introduction of new manufacturers of an active substance based on a CEP with deviations in additional specifications for impurities and product specific requirements cannot be filed as type IA/IB notification. A full documentation is needed to support a type II variation. Industry suggestion: Instead of "unchanged", the term of equivalent or tightened should be included. For the definition of equivalent, it is recommended to include the definition in US BACPAC I.
1. Sterile substance	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary.
2. Other substances	**IA**	• See change no. 15 b) no.1

Change	Classi-fication	Impact on industrial practice
c) Substance in veterinary products for use in animal species susceptible to TSE	**IB**	• See change no. 15 b) no.1
16. Submission of a new or updated TSE certificate of suitability for an active substance or starting material /reagent/intermediate in the manufacturing process of the active substance for a currently approved manufacturer and currently approved manufacturing process		• Change is newly introduced to the Annex I and reflects the handling of TSE CEP and the approach of raw material suppliers to certify their products for compliance with the TSE requirements • Industry opinion: These changes should require a simple notification to authorities to introduce the new CEP to the documentation and not a variation procedure. → see comment change no. 15 • The documentation no. 3: a document providing information of any materials falling under the scope of the *NfG on Minimising the Risk of Transmitting Animal Spongioform Encephalopathy Agents via Human and Veterinary Medicinal Products* including those which are used in the manufacture of the active substance, is questionable. It is a repetition of information already available in the TSE-CEP, hence an unnecessary duplication. This requirement seems to suggest that the applicant needs both, a TSE certificate and supporting data. The updated TSE table should be sufficient regarding a change for a particular substance (industry opinion).
a) Substance in veterinary medicinal product for use in animal species susceptible to TSE	**IB**	• Classified as "tell, wait and do" change → Evaluation by the RMS/Rapporteur is necessary for substances in veterinary medicinal products for use in animal species susceptible to TSE.
b) Other substance	**IA**	• Classified as "tell and do" change → Implementation after acknowledgement of a valid notification after 14 days. It is advantageous for industry.
17. Change in		

Change	Classi-fication	Impact on industrial practice
a) the re-test period of the active substance	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulation. Evaluation by the RMS/Rapporteur is necessary. • Biological products are excluded. A change on re-test period for biological products are managed as Type II variations → restriction compared to the former Variation Regulations. • Due to the reason that the change should not be made to an unexpected event during production and not be a result of stability concerns, the change is mainly focused on an extension of shelf-life. If the stability protocol was approved, then the quality determining parameters have been decided on, and the MAH just demonstrates that he complies with the requirements. No new assessment should therefore be needed and the change should be classified as type IA notification. This especially applies if a revised CEP has been obtained for a change in the re-test period, as the change will have undergone a prior review by an EDQM assessor. The appropriate stability studies would be performed and retained on site and evaluated during inspections.
b) the storage condition of the active substance	**IB**	• Classified as "tell, wait and do" change → the time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary.
19. **Change in specification of an excipient**		
a) Tightening of specification limits	**IA/IB**	See change no. 12 a)
b) Addition of a new test parameter to the specification	**IB**	See change no. 12 b) no. 1
20. **Change in test procedure for an excipient**		
a) Minor changes to an approved test procedure	**IA**	• Classified as "tell and do" change → the variation can be implemented in a shorter time compared to the former Regulations. • To file this change as a type IA notification according to the new Variation Regulation, the method of analysis should remain the same and no new impurities should be detected. This would require an evaluation of the change.→ see change no. 13 a). • No written declaration need to be submitted stating that the specifications of the excipients have not been changed.

Change	Classi-fication	Impact on industrial practice
b) Minor changes to an approved test procedure for a biological excipient	**IB**	• The requirements for changes in test procedures are stated as a separate category with different requirements in documentation compared to non-biological excipients. The change needs an evaluation to demonstrate that quality, safety and efficacy are not affected and comparative validation results showing that the amended test procedure is equivalent has to be provided.
c) Other changes to a test procedure, including replacement of an approved test procedure by a new test procedure	**IB**	See change no. 13 b)
21. Submission of a new or updated European Pharmacopoeia certificate of suitability for an excipient		• The change is newly introduced to the Annex I for excipients and reflects the approach of suppliers to certify the compliance of the excipients with the European Pharmacopoeia. • Industry opinion: see change no. 15 • Condition no. 2 requires unchanged additional (to European Pharmacopoeia) specifications for product specific requirements (e.g. particle size profiles, polymorphic forms). Unchanged additional impurities are excluded from this condition compared to the update of a CEP for an active ingredient.→ less strict for excipients compared to the active substance.
a) From a manufacturer currently approved	**IA**	• Classified as "tell and do" change → change can be implemented after acknowledgement of a valid notification.
b) From a new manufacturer (replacement or addition)		
1. Sterile substances	**IB**	• Classified as "tell, wait and do" changes. An evaluation from the RMS/Rapporteur is necessary to demonstrate that quality, safety and efficacy are not affected with a sterile substance from a new manufacturer. Sterile substances cause a higher quality potential compared to other substances.
2. Other substances	**IA**	• Classified as "tell and do" change → variation can be implemented after acknowledgement of a valid notification.
c) Substance in veterinary medicinal product for use in animal species susceptible to TSE	**IB**	• Classified as "tell, wait and do" change. An evaluation by the RMS/Rapporteur is necessary to demonstrate that the quality, safety and efficacy of the veterinary medicinal product for animal species susceptible to TSE are not affected.
22. Submission of new or updated TSE European Certificate of Suitability for an excipient		• See change no. 16

Change	Classi-fication	Impact on industrial practice
a) From a manufacturer currently approved or a new manufacturer (replacement or addition)	**IA**	• Classified as "tell and do" change → variation can be implemented after acknowledgement of a valid notification after 14 days.
b) Substance in veterinary medicinal product for use in animal species susceptible to TSE	**IB**	• Classified as "tell, wait and do" changes. An evaluation by RMS/Rapporteur is necessary to demonstrate that the quality, safety and efficacy of the veterinary medicinal product for animal species susceptible to TSE are not affected.
25. Change to comply with European Pharmacopoeia or with the national pharmacopoeia of a MS		• Condition No. 2 states unchanged specifications (additional to Ph. Eur.) for product specific properties. Instead of the term unchanged, the term equivalent should be included. For the definition of equivalent, it is recommended to use the one included in BACPAC I.
a) Change of specification(s) of a former non-European pharmacopoeial substance to comply with European Pharmacopoeia or with a national pharmacopoeia of a MS		
1. Active Substance	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to former Regulations. Evaluation by the RMS/Rapporteur is necessary. • Documentation 5: comparative dissolution profile data required for the finished product for at least one pilot batch. In the former documentation comparative dissolution profile data on at least 2 production scale batches were required → decrease in requirement.
2. Excipients	**IB**	• See change no. 25 a) no. 1
b) Change to comply with an update of the relevant monograph of the European Pharmacopoeia or national pharmacopoeia of a MS		
1. Active substance	**IA**	• Classified as "tell and do" change → variation can be implemented after acknowledgement of a valid notification (14 days) and can be implemented faster compared to the previous Variation Regulations. • The introductory statements of Annex I of both Variation Regulations state that there is no need to notify the competent authorities of a MS of an update of the Ph. Eur. or national pharmacopoeia of a MS in case that compliance with updated monograph is implemented within 6 months of its publication and reference is made to the "current edition" in the dossier of an authorised medicinal product. → filing in this way, would avoid a variation.

Change	Classi-fication	Impact on industrial practice
2. Excipient	**IA**	• see change no. 25 b) no. 1
26. **Change in the specifications of the immediate packaging of the finished product**		• Change is newly introduced to the Annex I
a) Tightening of specification limits	**IA/IB**	• Classified as "tell and do" change under the condition that the change is not a consequence of any commitment from previous assessments to review specification limits → variation can be implemented in a short time (14 days). • Classified as "tell, wait and do" change if the change is a consequence of a commitment from previous assessment.→ see comment change no. 12 a)
b) Addition of a new test parameter	**IB**	• Classified as "tell, wait and do" change. An evaluation of the new analytical method and validation data is needed. • Regarding exclusion of the NIRS-method from minor variations → see change no. 12 b) no. 1
27. **Change to a test procedure of the immediate packaging of the finished product**		
a) Minor change to an approved test procedure	**IA**	• See change no. 20 a)
b) Other changes to a test procedure, including replacement or addition of a test procedure	**IB**	• See change no. 13 b)
29. **Change in the qualitative and/or quantitative composition of the immediate packaging material**		• Biological products are excluded from the change → former Regulations did not exclude biological products; now stricter requirement. • Validation methods are not explicitly required for all new analytical methods of the packaging material. If new methods are introduced, the validation data have to be filed in the update of relevant sections of CTD/NTA Dossier. • Batch numbers of stability data have to be indicated, no written declaration is required anymore.

Change	Classi-fication	Impact on industrial practice
a) Semi-solid and liquid pharmaceutical forms	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary.
b) All other pharmaceutical forms	**IA/IB**	• Change is classified as a " tell and do"-change for all other pharmaceutical forms, except semi-solids and liquid pharmaceutical forms, if the change only concerns the same packaging type and material (e.g. blister to blister change). The documentation requires the amended sections of the CTD/NTA Dossier, stability studies (in the documentation only batch numbers should be indicated) and the comparative of the current and proposed specifications → change can be implemented easily in production and it is a facilitation to chose between different suppliers of the same packaging type and material. • Change is classified as "tell, wait and do"-change, if the proposed packaging type is at least equivalent to the approved material in respect of its relevant properties. Besides stability studies a proof must be provided that no interaction between the content and the packaging material occurs. This requirement is extended to all other pharmaceutical forms (in the former requirements, it was only for semi-solids and liquids necessary), if the change does not concern the same packaging type and material.
31. Change to in-process tests or limits applied during manufacture of the product		
a) Tightening of in-process-limits	**IA/IB**	• See change no. 26 a)
b) Addition of new test limits	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to former Regulations. Evaluation by the RMS/Rapporteur is necessary. • The documentation requirements are increased compared to the former requirements: In the former *Guideline on Dossier requirements for Type I Variations* a description of the analytical methodology and summary of validation was required, now batch analysis data on 2 production batches (for biological medicinal products 3 batches) are required additionally. These batches have to be manufactured prior to submission of the variation and can be sold after 30 days review time. • Regarding exclusion of the NIRS-method from minor variations → see change no. 12 b) no. 1
37. Change in specification of the finished product		
a) Tightening of specification limits	**IA/IB**	• See change no. 12 a)

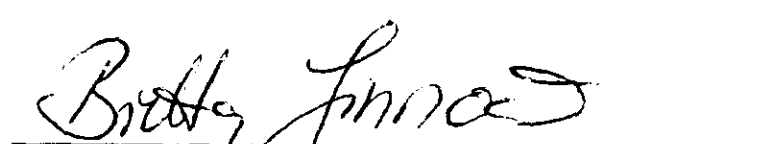
Change	Classi-fication	Impact on industrial practice
b) Addition of a new test parameter	**IB**	• Classified as "tell, wait and do" change. An evaluation of the new analytical method and validation data is needed. • Exclusion of the NIRS-method from minor variations → see change no. 12 b) no. 1
38. **Change in test procedure of the finished product**		
a) Minor change to an approved test procedure	**IA**	• See change no. 20 a) • Inconsistency with condition no. 4: the change occurs to an approved test procedure. The condition 4 excludes any new testing method concerning a novel non-standard technique or a standard technique used in a novel way. Maybe, it should exclude minor changes to an approved novel standard technique or a standard technique used in a novel way from type IA variation that should be filed as type II variation. It is not stated clearly.
b) Minor change to an approved test procedure for biological active substance or biological excipients	**IB**	• The requirements for changes in test procedures are stated as a separate category with different requirements in documentation compared to non-biological excipients. The change needs an evaluation to demonstrate that quality, safety and efficacy are not affected and comparative validation results showing that the amended test procedure is equivalent has to be provided. • Inconsistency with condition no. 4: → see change no. 38 a)
c) Other changes to a test procedure, including replacement or addition of a test procedure	**IB**	• See change no. 13 b)
42. **Change in:**		

Change	Classi-fication	Impact on industrial practice
a) the shelf-life of the finished product		• Change summarizes four changes from former *Guideline on Dossier Requirements for Type I Variation* (Changes nos. 20, 21, 22, 23). • Due to the reason that the change should not be made due to an unexpected event during production and should not be a result of stability concerns, the change is mainly focused on an extension of shelf-life. If the stability protocol was approved, then the quality determining parameters have been decided on, and the MAH just demonstrates that he complies with the requirements. No new assessment should therefore be needed and the change should be classified as type IA notification. A shelf-life reduction of the finished product resulting from a harmonisation process within the EU from 5 to 3 years should also be considered as type IA notification (industry opinion).
1. As packaged for sale	**IB**	• Classified as "tell, wait and do" change → time for the variation procedure is the same compared to the former Regulations. Evaluation by the RMS/Rapporteur is necessary
2. After first opening	**IB**	• See change no. 42 a) no. 1
3. After dilution or reconstitution	**IB**	• See change no. 42 a) no. 1
b) the storage conditions of the finished product or the diluted/reconstituted product	**IB**	• See change no. 42 a) no. 1 • Biological medicinal products are excluded from this variation and this change has to be filed as a type II variation → stricter requirements compared to the former Regulations.
44. Change in specification of a measuring or administrative device for veterinary medicinal products		• Change is only specified for veterinary medicinal products, i.e. this change has to be filed as type II variation for changing of the specifications of a measuring or administrative device for human medicinal product. On the other hand such changes would only be submitted to the authorities when the tests concerned are supplementary to the tests presented to obtain the CE mark. Such situations would occur so infrequent, that a variation would not seem to be necessary. Changes to or addition of tests, as part of the CE certification, should not be submitted to health authorities and do not appear in the variation Annex.
a) Tightening of specification limits	**IA/IB**	• See change no. 26 a)
b) Addition of a new test parameter	**IB**	• See change no. 26 b)
45. Change in test procedure of a measuring or administrative device for veterinary medicinal products		• See change no. 44

Change	Classi-fication	Impact on industrial practice
a) Minor change to an approved test procedure	**IA**	• See change no. 20 a)
b) Other changes to a test procedure, including replacement of approved test procedure by new test procedure	**IB**	• See change no. 13 b)
46. Change in the summary of product characteristics of an essentially similar product following a Commission decision for a referral for an original medicinal product in accordance with Article 30 of Directive 2001/83/EC or Article 34 of Directive 2001/82/EC (for Mutual Recognition Procedure only, Regulation 1084/2003)	**IB**	• Change is newly introduced to the Variation Regulations in order to file the amended SmPC/packaging leaflet and labelling as an outcome of the referral procedure.
46. Change in the summary of product characteristics, labelling and package *leaflet/insert as a consequence of a final* opinion in the context of a referral procedure with in accordance with Articles 31 and 32 of Directive 2001/83/EC or Articles 35 and 36 of Directive 2001/82/EC (for CP only, Regulation 1085/2003	**IB**	• Change is newly introduced to the Variation Regulations in order to file the amended SmPC/packaging leaflet and labelling as an outcome of the referral procedure.
47. Deletion of: (for Centralised Procedure, Regulation 1085/2003)		• Change is newly introduced to the Variation Regulations in order to notify changes of a pharmaceutical form, strength and pack sizes of the medicinal product of the MS to the EMEA
a) a pharmaceutical form	**IA**	• Classified as "tell and do" change, can be implemented after receiving the acknowledgement of a valid notification.
b) a strength	**IA**	• Classified as "tell and do" change, can be implemented after receiving the acknowledgement of a valid notification.
c) a pack-size(s)	**IA**	• Classified as "tell and do" change, can be implemented after receiving the acknowledgement of a valid notification.

[2], [3], [4], [5], [6], [13], [15], [17], [25] [37], [38], [39]

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



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