Change Control Systems in Europe – how are they influenced by Regulation EC 1234/2008 and Directive 2009/53?

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

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List of Abbreviations

AMG	Arzneimittelgesetz
API	Active Pharmaceutical Ingredient
BAH	Bundesverband der Arzneimittelhersteller, Germany
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte, Germany
BPI	Bundesverband Pharmazeutischer Industrie, Germany
CA	Competent Authority
CAPA	Corrective action and preventive action
CEP	European Pharmacopoeia Certificate of Suitability
CHMP	Committee for Human Medicinal Products
CMD (h/v)	Coordination Group for Mutual Recognition and Decentralised Procedure (human/veterinary)
CMS	Concerned Member State
CP	Centralised Procedure
CR	Commission Regulation
DCP	Decentralised Procedure
DE	Germany
DDPS	Detailed Description of Pharmacovigilance System
EC	European Commission
EMA	European Medicines Agency (former EMEA)
EP	European Parliament
EU	European Union
GMP	Good Manufacturing Practice
HMA	The Heads of Medicines Agencies
ICH	International Conference on Harmonisation (EU, Japan, USA)
ISO	International Organisation for Standardisation
MA(H)	Marketing Authorisation (Holder)
MR(P)	Mutual Recognition (Procedure)
MS	Member State
NtA	Notice to Applicants
OJ	Official Journal
PI(L)	Product Information (Leaflet)
PIC	The Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products
PMF	Plasma Master File
PQR	Product Quality Review

PSRPH	Potential Serious Risk to Public Health
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RA	Regulatory Affairs
R&D	Research and Development
RMS	Reference Member State
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
UK	United Kingdom
USA	United States of America
USR	Urgent Safety Restrictions
VAMF	Vaccine Antigen Masterfile

1 Introduction

The pharmaceutical industry is undergoing **massive change processes** driven by changes in regulatory framework, new knowledge regarding safety of a product or even a product class. Furthermore changes resulting from acquisitions, mergers, outsourcing or new technologies are getting more and more important. Companies are combining their workforces and globalising their processes, with the main intention to be competitive in global market or even to be able to survive.

While reducing the costs to remain competitive, **control over their quality systems** must be maintained. This implicates that product quality and regulatory compliance always needs to remain on a constant level or even should be increased. Additionally, introduction of new technologies with the aim of continuous improvement need to be managed within the quality systems across a variety of partners. Any change can have positive or negative effects during the product life-cycle.

Therefore, it is evident that companies need to run an efficient change control system suitable for **tracking, ensuring proper evaluation and implementation of changes**. Time needed for implementation is increasing with the degree in change complexity (e.g. if multiple products or multiple countries are affected). Involving multiple contract service providers in one change – each following own processes and procedures – will exaggerate complexity of the change process additionally.

Each change control procedure implicates an impact assessment on the registration file of approved products. Not all of these changes are resulting in the need of submission of **variations (or notifications)** to competent authorities. Variations need to be submitted for any amendment to the approved registration file. Not submitting a variation, i.e. changing the registration dossier in course of a change process, will lead to chargeable, incompliant batch release by the responsible Qualified Person.

This master thesis will lay special focus on changes with regulatory relevance. Furthermore, it will highlight how European Change Control systems are influenced by **Variation Regulation EC 1234/2008 and Directive 2009/53**.

2 Issues under Examination

2.1 Regulatory Framework of Quality Management Systems

The main task of each **Quality Management System** is to assure and improve quality of processes and products/services. According to EC GMP guide part I chapter 1, there must be a comprehensively designed and correctly implemented system of **Quality Assurance** (QA) incorporating GMP, QC and Quality Risk Management. QA is covering all matters that might have influence on product quality.

Quality Management Systems can for example be certified according to **ISO 9001 rules** by accredited certifiers. ISO 9001 rules are recommendations / technical standards describing the requirements of quality management systems, which are based on a process-oriented approach. The aim is a continuous improvement of the quality management system, taking into account customer´s needs and requirements. ISO 9001 rules are also valid for target groups other than the pharmaceutical industry.

PIC/EU-GMP guidelines result from current drug law regulations supervised by authorities (e.g. EMEA) and are special rules for the pharmaceutical industry. “GMP ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation or product specification”.

The **GMP guide** consists of two parts: **Part I** describes rules for manufacturing of medicinal products for human and veterinary use, **Part II** describes rules for active substances used as starting materials. Some differences between EU demands and USA demands do exist in Part I, but Part II is completely harmonised in ICH region. The EC GMP guide consists of **20 annexures** mainly valid for finished dosage forms (Part I). **Annex 15** (Qualification and Validation) defines standards for GMP-conform documentation of changes.

Annex 20 (Quality Risk Management) of GMP guide was implemented in March 2008 as an adoption to ICH Q9 guideline providing internationally acknowledged risk management methods and tools that can be implemented optionally in pharmaceutical companies. Quality Risk Management is a systematic process for the identification, analysis, evaluation, communication and review of risks for the quality of a medicinal product.

2.2 Change Control / Change Management

According to ICH Q10, **Change Control** (Change Management) is a key quality element of of Quality Management Systems: “Innovation, continual improvement, the outputs of process performance and product quality monitoring and CAPA drive change. In order to evaluate, approve and implement these changes properly, a company should have an effective change management system”. From ICH Q10 point of view, all changes should be evaluated by a company´s **Change Control System**.

A change is a **planned action** to make things or procedures different, to alter, replace or modify things as well as to transform or substitute things or procedures. Changes differ from so-called **“planned deviations”,** which can only be regarded as short-cuts for alternatively using a proper change control procedure. “Real” **deviations**, on the other hand, are unplanned aberrations from an approved instruction or established standard. These deviations are legally accepted once they are reported, investigated for the potential root cause, classified, evaluated and trended. For these deviations, corrections and preventive actions (CAPAs) should be defined.

Change control is a **formal process** for **an elaborate assessment** of all announced or planned changes. It ensures that intended changes to a product (or system) are introduced in a controlled, coordinated and effective manner, i.e. that they are authorised and completely documented before implementation and release to the market. This process must be well-documented in a reproductive and traceable way to meet the rules of Good Documentation Practice and Archiving. Not adequately-documented changes might always be a reason for findings during GMP inspections from the authorities. Change approval and implementation process is getting more and more complex, once regulatory filing is required or if regional requirements need to be taken into account.

According to **Annex 15 to EU Guide on Good Manufacturing Practice,** “all changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. The need for, and the extent of re-qualification and re-validation should be determined”. Assurance has to be taken, that no unintended consequences of a change will occur. Each change process should include a decision about relevance, ideally accompanied by a well-documented risk analysis.

It is recommended to include **document changes** into a change control system, especially if regulatory-relevant changes occur. Other issues in evaluation of the change may also be

included into the change approval process. Only if all functions involved in the process are working together, the process will run efficiently and fast enough to benefit from the change.

The complete change control process should be visualised in **a standard operation procedure (SOP)** describing the actions to be taken once a change is proposed. As this document has instructive character, it should be drafted by experts as well as reviewed and approved by QA. Personnel should be trained on the current valid version of SOP Change Control.

Different **types of changes** may exist: e.g. design changes, process changes, documentation changes or equipment changes. Beside these usually product-related changes, also IT- or administrative changes may appear. The company should take the decision to include all changes in one change control system or to have different change control systems running in parallel for product-related and not-product-related changes.

This master thesis will focus on **changes to medicinal products** and will not discuss changes regarding IT-, processes (e.g. SOPs) or administrative changes.

2.3 Triggers of change control process and general rules to be taken

Changes to medicinal products can result from **different triggers**:

- Marketing issues (e.g. pack size changes, change of product portfolio and volumes)
- Economical considerations, sourcing problems (e.g. material cost, decay of suppliers)
- Manufacturing and quality issues (e.g. poor robustness of related processes)
- Safety Issues / New Developments (e.g. USR, PI and SPC changes)
- Authority demands (e.g. graduate plans, renewals)

Some changes can not be avoided **if the MA holder has no choice** (e.g. if a supplier is not able to deliver any longer). Other changes may occur, where the applicant has the **option to change or not** (e.g. change in sites or equipment). Even minor changes or those considered to be minor, can have a big **impact on product quality or regulatory compliance**, especially if not properly controlled. All consequences of change need to be considered: changes with the previous intention of improvement can create other related problems or even result in a disaster.

The following **general rules or issues should be taken** into account for each change control process:

1. Quality risk management should be part of the change evaluation process. Effort and formality in evaluation should be **adapted to the level of risk**.

2. Changes in the pharmaceutical manufacturing practice area should always be evaluated regarding their **GMP-relevance** – always including a risk assessment.

3. **Design space** should be regarded, where applicable.

4. **Regional requirements** have to be taken into account for evaluation, if regulatory filing is required.

5. **Departments, customers or manufacturers** potentially affected by a change should always be informed or even requested for their change approval before implementation.

6. Technical justification and **expertise from all relevant disciplines** (e.g. R&D, Manufacturing, Quality, RA or Medical) should be included in change evaluation, if requried. In this course, **prior knowledge** about product development, stability reports, validation reports, scale-up processes or tech transfers should always be included into the risk analysis (ICH Q9). This knowledge can possibly reduce the demand or extent of revalidation issues for a new change.

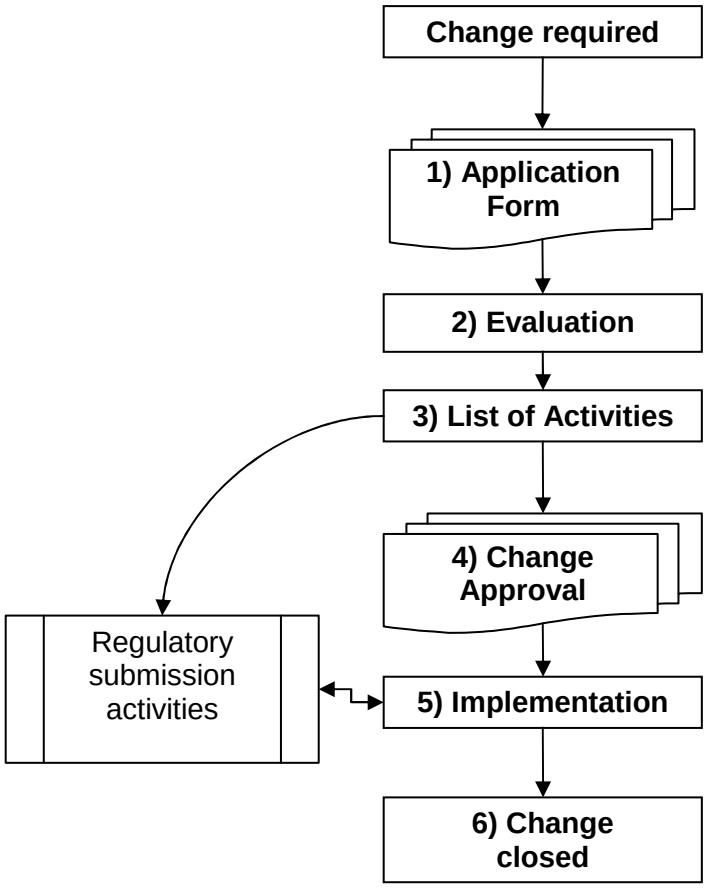
7. Before implementation and change closure, it should be evaluated, if all pre-defined change objectives and evaluation criteria have been fulfilled and **no deleterious effects on product quality** have occured.

8. A **post-implementation review** should be conducted in case of changes with a potential impact on quality, efficacy and safety of the product. This for example applies to quality-relevant changes requiring a type II variation. Since it is compulsory to review each change carried out to the processes or analytical methods within the frame of the Product Quality Review of a product, this post-implementation review could **be included into each PQR**, if applicable.

9. Change Control / Change Management should **cover the whole life cycle** of one product beginning with pharmaceutical development, followed by technology transfer activities, commercial manufacturing and even until product discontinuation.

2.3.1 Change Control Process Flow Chart

The following **flow chart** describes the key process steps usually included in each change control process:



1) The initiator of a change request should fill in a formal request (**application form**) for the issue to be changed, including a description and justification for change necessity. The change request should be recorded in Change Control system by assigning a number and it should be categorised with regard to its importance, priority, impact and complexity.

2) **Evaluation** (impact assessment) should always be done by the site´s change control committee performing a risk analysis. This is typically done by answering a set of questions concerning potential risks on quality, efficacy and safety of the product. The analysis of risk versus benefit should be done according to ICH Q9.

   Impact assessment should also include a cost/benefit analysis and a judgement, which personnel should carry out the change.

3) The **list of activities** (implementation plan) should be pre-defined by decision-making personnel to describe the consequences of the respective change in detail. Timelines, extent and responsibilities for operational steps need to be defined, e.g. preparation of pilot batches, requirement of (re-)validation or document updates.

4) All affected areas as well as third parties (such as customers or contract manufacturers) need to be integrated into evaluation and the **change approval** process. The change request can be regarded as approved once quality assurance as final decision-making department has signed the change request. The Qualified Person (QP) in person does not strictly need to sign each change control form, since all changes need to be included into the Product Quality Review (PQR), the QP has to sign anyway.

5) Regulatory submission can be part of the list of activities. **Implementation** of the steps (defined in the list of activities) can start “at risk” before regulatory submission, but regulatory approval (if required) must be available before placing the product on the market. The change should be declared as implemented, if the final benefit of change matches the intended benefit, previously defined in the list of activities.

6) After agreement that the change was implemented correctly and all change control activities are appropriately documented, the **change** can be **closed.**

2.3.2 Evaluation of change by expert teams

The change Control **decision board** should be composed of cross-functional individuals. Based on risk consideration (level of risk), the group dimension should be adapted. The higher the level of risk, the higher the amount of personnel to be included into the decision process.

GMP-relevant changes should be handled including a **complete review and approval of QA** and any other department that might be impacted by the change. Expert groups need to define timelines, activities and responsibilities in an implementation plan clearly. This implementation plan should also define the conditions when a change can be regarded as implemented.

Evaluation by expert teams should focus on the following exemplary questions:

- Necessity of change in general?
- Does the change have an influence on quality, safety and efficacy of the product?
- Is the cost/benefit analysis positive or is the change inevitable for further placing the product onto the market?
- Do legal issues (e.g. patent issues or contracts) have to be taken into account?
- Necessity of additional stability studies?
- Does the change have influence on validation or qualification issues?
- Requirement of GMP document updates?
- Necessity of RA notifications or even variations to competent authorities (update of the registration file)? What timelines will result from this?
- What parties need to be informed / to give their approval before start of implementation or even before change approval?

2.3.3 Responsibilities of parties involved

In the Change Control System, personnel responsible for single tasks as well as QP-involvement needs to be pre-defined previously in the **SOP Change Control.** Responsibilities of involved parties can differ from company to company, but the main princible should be comparable.

Site Management is responsible for ensuring that any modificaton to operations is evaluated, approved and documented from a technical, scientific, quality and RA point of view.

Quality Management (QM) is responsible for ensuring a robust and easy-to-handle Change Control system assuring the involvement of all needed functions. This includes a clear definition of roles and responsibilities of initiator, reviewer and approver. A simple procedure illustrated by flow charts needs to be created. Training and education of all employees involved in the change control system should be carried out focussing on the serious potential for negative impact of any uncontrolled change. A **coordinator responsible for leading the change process** should be assigned by the responsible department.

The **initiator of a change request** should fill in an application form addressing the issue to be changed and forward it to the coordinating change control group (usually in QM department). The responsibility for technical or scientific evaluation of a change is with the **concerned departments.** If there is an impact on the dossier, the proposed change must be reviewed by **Drug Regulatory Affairs** for the need of supportive data required for dossier amendments. The appropriate regulatory function must submit the provided documentation to the authorities.

The **Site Quality Manager** is responsible for ensuring that there are systems and procedures in place that comply with the written procedure (SOP). The person is also responsible for approving/rejecting a proposed change at site level following an assessment by a Change Control Committee at the site. Furthermore, the **Site Quality Manager** is responsible for the quality evaluation of the respective change. Regulatory evaluation is also under his responsibility, in cooperation with a **regulatory representative**.

Site Quality Management should be responsible for coordinating change control activities in their respective areas ensure the assessment of all proposed changes and the communication of change approval to all affected parties. It must ensure that RA evaluation captures any potential impact on the registration file. If a change has no regulatory impact, implementation and closure of the change is handled by the Site Quality Management.

2.4 Explanatory notes to Commission Regulation (EC) No 1234/2008

Variations are by definition any amendment (i.e. addition/deletion/changing the content) to the documentation representing the legal basis for each Marketing Authorisation (MA) of a medicinal product. Any amendment of documentation needs to follow rules specified in European legislation or guidelines. Amendments to documentation not being part of the registered documentation do not trigger a variation.

The Review of former Commission Regulations 1085/2003 (central MA´s) and 1084/2003 (Mutual Recognition MA´s) from June 2003 resulted in the development of the new **Variation Regulation (EC) No 1234/2008.** This regulation was generated with the aim to “establish a simpler, clearer and more flexible legal framework for the handling of variations while ensuring a high level of public and animal health” while not departing from general principles. The initial intention to cover all purely national marketing authorisations with this regulation from 01 January 2010 on, could not be fully achieved (see also: “Content of Directive 2009/53/EC of the European Parliament and of the Council”).

For reviewing of this new Variation Regulation the **Comitology Regulatory procedure** had to be followed. After final discussion and voting at the Standing Committee on 10 June 2008 the scrutiny process at EP was running until 13 September 2008. The proposal was adopted by EC and published on 12 December 2008 in the OJ. 20 days after publication CR (EC) 1234/2008 entried into force on 01 January 2009. Effective date of Variation Regulation was 01 January 2010 (12 months after entry into force).

According to Article 4(1) of Regulation 1234/2008, **guidelines on the categorisation of changes and operational procedures** were published to specify the high-level classification of Variation Regulation more precisely. These guidelines are described in chapter 2.6.

The following types of changes are not addressed by Variation Regulation 1234/2008 and have **to be proceded according to national law** (procedure was not changed with this new regulation):

- **transfer of MA** from one MAH to another according to Commission Regulation EC No. 2141/96 (see also Article 1 (2) of Variation Regulation)
- changes in labeling and package leaflet without connection to the content of the SPC (Directive 2001/83/EC **Art. 61, section 3**).

Additional national rules do exist, but they are not examined in detail in this master thesis.

2.5 Main changes caused by Commission Regulation (EC) No 1234/2008

To enable the authorities to focus on variations with a potential impact on quality, safety or efficacy and to reduce the overall amount of variation procedures, the following innovations were introduced in course of the new Variation Regulation 1234/2008:

- Introduction of a European **annual reporting system** (**do and tell procedure**)
- Possibility for **grouping of variations**
- Reduction of duplicate work by using a **worksharing procedure**
- Implementation of **design space** concept according ICH.
- Type **IB by default** for previously not defined variations and **safeguard clause**

In case of **unforeseen variations (Article 5 of Regulation)**, MAH or CA can request the CMD (or the EMA in case of central MAs) for recommendation on classification of previously

unclassified variation. Response should be delivered within 45 days and variation submission should be done until pre-defined submission dates.

Over all, **Coordination Groups** (CMDh/v) are requested to increase cooperation between Member States. They are empowered to give scientific recommendations on unclassified variations (in consultancy with EMA), for coordination of worksharing and for processing of referrals for type II variations and worksharing procedures, if a CMS has raised PSRPH.

Furthermore, **harmonisation of procedure** was intended to be achieved by Regulation (EC) 1234/2008 for national authorisations as well. This previous aim could not be fully achieved for MAs granted before 1998. Furthermore, harmonisation was not fully reached since some national authorities follow the new regulation, but use different timelines. Please also refer to chapter 2.7 describing the impact of Directive 2009/053/EC.

2.5.1 Annual Reporting System and immediate notifications (IA_{IN})

According to Article 8 of the Variation Regulation, a European **annual reporting** system for grouping of certain minor variations was introduced (**do and tell variations**).These variations do not require prior approval and should be notified to the respective competent authority at any point in time, but at the latest 12 months after implementation of the first type IA variation. These notifications should be combined with upcoming variations or other regulatory actions. Minor variations with higher priority should be notified to the national competent authority or EMA **immediately following implementation (type IA_{IN})**. One example for type IA_{IN} notificiations is a change in releasing site for a medicinal product.

2.5.2 Grouping of Variations

In certain cases, **grouping of variations** is now allowed to facilitate the review of variations and reduce administrative burdens. Annex III of Variation Regulation 1234/2008 defines the different optional possibilities to group variations of the same MA holder in one application:

- Several changes to one MA
- Identical changes to several MA´s
- Several identical changes to several MA

The “**same MAH**” was previously described in Commission Communication 98/C229/03 as follows: “Applicants belonging to the same mother company or group of companies and applicants having concluded agreements or exercising concerted practices concerning the

placing on the market of the relevant medicinal product". As agreed on CMD(h) level, an **MA is defined through its MR-number** (inclusion of all strengths, e.g. DE/H/1234/001-009).

As described in Annex III and Article 7 of this regulation, **not only type IA variations** are suitable for grouping: also type IB and type II variations can be grouped in special cases. If single changes of one group are rejected, applicant can decide to withdraw them from an application. If no consensus is reached between MS concerned regarding single aspects, the complete variation complex is suspended until decision is reached.

The variation type of grouped variations has to be classified according the **highest level of the individual submission type**. Grouping of variations for more than one MA can only be done in case of **same RMS**. If RMSs are different, the worksharing procedure has to be followed. It is recommended to inform RMS or EMA about a planned grouped variation not listed in Annex III **2 months in advance**. Otherwise the RMS can refuse the respective variation application stating that a prior agreement was not requested before submission.

2.5.3 Worksharing Procedure

Using the worksharing procedure, duplicate work in submission and evaluation of variations can be avoided. A worksharing procedure according to Article 20 of Variation Regulation can be applied to **type IB, type II and for grouped variations** covering several MA´s **owned by the same MA holder**. An extension application can not be run through worksharing procedure. Type IA variations are also excluded from worksharing procedures.

The **documentation** related to a variation must be the same for every worksharing procedure – otherwise separate single applications are required. If classification types of variations in one worksharing project are different, procedure acts in pursuance with the **highest classification level** implicated.

Coordination of this procedure will be conducted by the EMA if one central MA is included or by the CMD (h/v) in all other cases. **Evaluation** in a worksharing procedure has to be performed by the reference authority, i.e. Scientific Committees (e.g. CHMP) for central MAs or the competent authority of a Member State concerned, previously chosen by CMD. For the latter process, previous recommendation for a procedure-specific reference authority by the MAH should be taken into account. It is recommended to get in contact with EMA or CMD as well as the proposed reference authority in order to inform about submission purpose (**at least 3 before submission**).

After variation submission to all CA concerned, the application is validated by the reference authority. Subsequently, the decision process will follow with a **timeframe of a type II**

variation. Excluding the possibility of a clock stop, scientific opinion can be awaited after 60 days for standard procedures, after 30 days for safety issues or after 90 days for extension applications (e.g. change or addition of therapeutic indications). These timelines can be extended, if request for supplementary information is received from the reference authority.

In case the decision from the reference authority is not accepted by concerned authorities within 30 /(60) days, or potential serious risk to public health (PSRPH) is raised, a **CMD- or CHMP-referral** procedure will follow subsequently. A referral procedure can not be raised by the applicant himself.

2.5.4 Design Space

Design space can be regarded as a multidimensional combination and interaction of input variables and process parameters. Resulting from an ICH activity to facilitate continuous improvement of manufacture, modern tools (**ICH guidelines Q8** (Pharmaceutical Development), **Q9** (Risk Management) or **Q10** (Pharmaceutical Quality System)) were implemented to achieve this aim.

Design space should provide **more flexibility** for a manufacturer performing manufacture of a medicinal product within an approved design space. Every design space proposed by the applicant is subject to regulatory assessment and approval. Working within an approved design space leads to a reduction of post-approval variations that would have to be submitted to competent authorities otherwise. Only if limits of any approved desgin space are exceeded, changes requiring evaluation and variations will come up. According to Annex II (classification of variations) introduction of a new design space or extension of an approved one will result into a **type II variation**.

2.5.5 Type IB by Default and Safeguard Clause

If a change is not listed in Annex II of Variation Regulation, not described in the guideline on the details of the various categories of variations and also not pursuant to recommendation on unforeseen variation (article 5), it should be treated as minor variation of type IB (**type IB by default**). Apart from this, it is the decision of RMS to change classification of this type IB variation to a type II variation (after 7-day objection period of CMS) in case of significant impact on quality, safety or efficacy of the medicinal product concerned (**safeguard clause**).

2.6 Guidelines resulting from Regulation 1234/2008/EC

The Variation Regulation lays down general rules on the types and classification of variations in **Articles 2 and 3 and in Annex II**. Additionally **Article 4 (1) (a)** charges the Commmission with the task of drawing up “guidelines on the details of the various categories of variations”. **Article 4 (1) (b)** charges the Commission to set up “guidelines on the operation of the procedures laid down in Chapters II, III and IV of Variation Regulation as well as on the documentation to be submitted pursuant to these procedures”. Both guidelines are valid for human and veterinary medicinal products.

Guidelines on the categorisation/classification of changes and operational procedures were published to specify the high-level descriptions of the Variation Regulation more precisely: according to Article 5 procedure, guidelines need to be **updated regularly** with respect to scientific and technical progress and recommendations on unforeseen variations.

The **actual processing system of variation procedures** (type IB and type II variations, extensions, USR´s and variations to human influenca vaccines) has not been changed. National “specialities” (e.g. co-marketing issues, hospital packs, MAH transfer) as well as changes to registered homeopathic and traditional herbal medicinal products will remain outside the scope of the new Variation Regulation and will further apply to national requirements, independent from the origin of an MA.

2.6.1 Categorisation / Classification Guideline

The classification guideline gives details on the variation classification into the categories defined in Article 2 of the Variations Regulation:

- Minor variations of type IA (e.g. administrative changes / with low impact on quality)
- Minor variations of type IB (e.g. shelf life extension)
- Major variations of type II

In addition to the high-level classification of **type IA** and **type II changes** in the Variation Regulation, this guideline completes the list of **type IA/IA$_{IN}$ changes** as well as type II variations. Some variations in this guideline are agreed examples of type IB variations. Changes unlisted are **type IB variations by default**. The competent authority (CA) can decide to upgrade a variation defined as IB by default to a type II during validation in case a significant impact on quality, safety or efficacy of the product is considered.

The classification guideline provides more detailed information on **conditions to be fulfilled** and **documentation to be submitted** in parallel with any variation application. For IB and type II variations, it also defines that supporting data to be submitted depends on the specific nature of the change.

General documentation requirements are also described in Annex IV of the Variation Regulation or in the Procedural Guideline (see also chapter 2.5.2). **Conditions and documentation** to be supplied for each variation number and procedure type can be regarded as comparable but not equal to the previous guideline. However, requirements for conditions and documentation have partly been changed compared to the previous guideline. These changes always need to be included in the regulatory evaluation of each change control process.

The Categorisation Guideline does not deal with the classification of **extensions** and refers to the definitions in **Annex 1** of the Variations Regulation.

The classification system of variations to medicinal products remains risk-based, depending on the level of risk to public or animal health and the impact on quality, safety or efficacy of the medicinal product concerned. The highest potential impact leads to a complete scientific assessment - similar to the evaluation of a new MA.

The Classification Guideline **differentiates changes regarding its scope:**

A) Administrative changes,

B) Quality changes (active substance, finished product, CEP/TSE/monographs, PMF/VAMF, medical devices),

C) Safety, efficacy and pharmacovigilance changes.

D) Specific changes to PMF / VAMF changes

Each topic is described by means of an own chapter. In the guideline each of these chapters contains an annex including a **list of variations** to be classified as minor or major variation. Such a list also defines minor variations requiring immediate notification according to Article 8(1) of the Variation Regulation.

Where reference has to be made to specific variations of this guideline, the variation should be **quoted using the structure: X.N.x.n.** One example might be variation B.I.a.3 for a “change in batch size (including batch size ranges) of active substance or intermediate”. This

new system has replaced the former system of consequential numbers and is more flexible, once new classifications not defined in the first version need to be included.

Furthermore, this guideline gives additional information on special changes:

- Adaption to a **new monograph of European or national pharmacopoeias** does not require notification to the authorities if new specification or method is implemented 6 months after its publication and the dossier references to the *current edition* of pharmacopoeia.

- Each change to the content of a dossier supporting a European Pharmacopoeia Certificate of Suitability (CEP) needs to be submitted to the European Directorate for the Quality of Medicines (EDQM). **Revision of a CEP** leads to a need of notification by every MAH affected.

- After changes to a Plasma Master File **(PMF)** or Vaccine Antigen Master File **(VAMF)** according to Chapter D of this Guideline, each MAH will have to update his documentation in accordance with Chapter B.V of this Guideline.

- **Editorial changes** may be included into later variation applications of the affected part of the dossier and do not require single application.

- The Classification Guideline has taken into account the NtA **"Guideline on the categorisation of extension applications** versus variation applications" but does not replace it. Therefore, it should also be taken into account.

- Changes within a **design space** do not require a notification or variation.

2.6.2 Operational / Procedural Guideline

This "Guideline on the operation of the procedures laid down in Chapters II, III, and IV of this Regulation as well as on the documentation to be submitted pursuant to these procedures" has the aim to facilitate the interpretation and application of the Variation Regulation.

This guideline applies for the **following types of MAs** (Article 1 (1) of Variation Regulation):

- Authorisations granted in accordance with Council Directive 87/22/EEC, Articles 32 and 33 of Directive 2001/82/EC and Articles 28 and 29 of Directive 2001/83/EC and Regulation (EC) No 726/2004.

- Authorisations granted following a referral, as provided for in Articles 36, 37, 38 of Directive 2001/82/EC or Articles 32, 33 and 34 of Directive 2001/83/EC which has led to complete harmonisation.

Variations to the terms of marketing authorisation granted following purely national procedures are excluded from the scope of this guideline.

This guideline covers minor variations of type IA and IB, major variations of type II, extensions and Urgent Safety Restrictions (USRs). Timeframes have not been changed. This guideline provides **details** regarding submission, grouping and handling of these appplication types. Not all of those details will be discussed in this master thesis. Only those having a potential influence on change control systems are highlighted.

2.7 Content of Directive 2009/53/EC of the European Parliament and Council

Directive 2009/53/EC was agreed on the European Parliament and the Council (Co-decision procedure for the amendment of Directives) and **published** in the Official Journal (OJ) **30 June 2009.** Directive 2009/53/EC is amending Directive 2001/82/EC and Directive 2001/83/EC and should be transponed into national law after transposition time.

The main aim of Directive 2009/53/EC was to enable **harmonisation of Community procedures** for variations with regard to the different types of marketing authorisations. The harmonisation of rules was conducted in order to reach legal consistency, to reduce administrative burden and to strengthen predictability for economic operators. The majority of medicinal products for human or veterinary use currently on the market has been authorised under purely national procedures and is not covered by Regulation 1084/2003. Variations to national marketing authorisations have been processed according to national rules.

In Article 1 of this Directive 2009/53/EC, amendments to Directive 2001/82/EC and Directive 2001/83/EC are initiated assigning the European Commission to "adopt appropriate arrangements for the examination of variations to the terms of marketing authorisatios granted in accorance with this Directive". Adoption has to be reached by implementing the Variation Regulation (1234/2008/EC). One example for simplifying the administrative procedure is the possibility to submit one single application for one or more identical changes which apply to more than one marketing authorisations.

Special topics from **Article 2 of Directive 2009/53/EC** are the following :

- Sub-paragraph 4 to amended Article 24b of Directive 2001/83: "A Member State may continue to apply national provisions on variations applicable at the time of entry into force of the implementing regulation to **marketing authorisations granted before 1 January 1998** to medicinal products authorised only in that Member State. Where a medicinal product subject to national provisions in accordance with this article is subsequently granted a marketing authorisation in another Member State, the implementing regulation shall apply to that medicinal product from that date."

- Subparagraph 5 to amended Article 24b of Directive 2001/83: "Where a Member State decides to continue to apply national provisions pursuant to paragraph 4, it shall notify the Commission thereof. If a **notification has not been made by 20 January 2011, the implementing regulation shall apply.**"

The content of these two Articles has special influence on the variation notification system of Member States that have run independent national notification systems (e.g. §29 of German

Drug Law or system in Austria). Also member states with a categorisation of changes according to CR 1084/2003 but different time lines are affected by this Directive. Few countries (e.g. UK or member states that joined the EU after 2005) already had implemented CR 1084/2003 before. The CMDh homepage provides the list **"**Implementation of Variation Regulation 1234/2008 in each Member State for Medicinal Products authorised by purely national procedures". The intention of this list is to provide a brief summary on the **status of implementation of new Variation Regulation** for national procedures in the member states.

If any Member State decides to notify the Commission of their continuation of applying national provisions, it should take into account that it will have two different systems for submission of variations running, depending on the date and type of granted marketing authorisation: the first for the purely national products with a registration date before 01 January 1998 and the second for all other products.

In case of Germany, the decision to use the option is further pending (status June 2010). The German association BAH is currently requesting its member companies for **estimation of the precise number of affected MAs.** Basing on data from 1997, estimates show, that the open decision will have an effect on a considerable amount of approx. 10.000 MAs (if withdrawn or rejected MAs or those included into an MR procedure are excluded). BAH is of the opinion that the more flexible **§29 of German Drug Law (AMG)** has several advantages over the European Variation System and should not be completely replaced for licences authorised nationally before 01 January 1998. Advantages of the terminatory system of §29 AMG are that requests on unclassified variations are unnecessary and implicite approval is reached 3 months after receipt by the authority (if authority does not contradict). Furthermore, safety-relevant addition of side effects, interactions or contraindications only require notification and thus can be implemented in an unbureaucratic way enabling a quicker provision of the new information to doctor and patient. Therefore §29 AMG serves a higher legal certainty to the MAH. In May 2010, **BAH and BPI have proposed a system for standardisation of variation and §29 AMG:** the above mentioned advantages of §29 AMG should be maintained, but change aspects should fulfill classification and documentation aspects of "Classification Guideline".

National licences authorised after 01 January of 1998 will have to follow the new European variation system. This can only be done after integration of these licences into Regulation 1234/2008 and implementation of Directive 2009/53/EC into national law. Careful prognoses let assume that the related date might be not until 2012.

3 Discussion

3.1 Triggers of change control activities and factors for optimisation

Each change in the regulatory environment of medicinal products has influence on Quality Management Systems. The influence of the new Variation Regulation 1234/2008 on a company´s change control system can be regarded as significant, since this **legislation has a big impact on the different steps of each change control procedure**, escpecially those including the necessity of regulatory submission activities.

With increasing cost pressure in the pharmaceutical market resulting from rebates to be provided to health insurance companies or other cost reduction tools of the legislative bodies, each company needs to search for **alternatives of cost reduction**. This is often resulting in buying alternative, cheaper raw material or facing the requirement of outsourcing their products to low-wage countries, such as India and China. The need of maintaining product quality on a similarly high level and taking into account GMP requirements is reflected in current GMP issue of the API supplier Glochem in India (GMP compliance issues in the production of Clopidogrel besilate). The requirement of **supplier qualification** prior to changes in suppliers of ingredients (such as active substances and other excipients) is getting more and more essential. Each change to a product can lead to a „paradise or disaster“.

From an economic point of view, each change control procedure can cause costs resulting from additionally required stability studies, (re-)validation issues, transfer activities, transports, as well as regulatory submission. Apart from these **direct costs,** additional manpower is required for realisation of each change intention. These costs always need to be taken into account before consideration of decision on a respective change. **Cost-benefit ratio** should always be positive.

Changes can also cause negative cost/benefit ratios in case of **inevitable authority demands** that need to be implemented mandatorily in order to maintain the respective marketing authorisation. One example might be changes arising after a graduate plan: product information (leaflet, SmPC and/or labelling) might need to be changed. Regulatory costs and replacement of existing packing material might result from this trigger.

In case of non-regulatory relevant changes (not requiring RA submission activities), only quality-related costs and demands will remain.

According to NfG on Manufacture of the Finished Dosage Form a “very detailed description of the manufacturing process should be avoided”. This shows the need of **generally-written**

dossiers and can be extended to the complete module 3 of the registration dossier, especially part 3.2.P.5 (analytical procedures): the lower the amount of regulatory relevant changes, the lower the costs for regulatory submissions.

This implicates the necessity for not “just copying & pasting” of GMP-relevant documents into the dossier. This might be easier to handle initially for the first dossier to be submitted, but with each document review the dossier would also be needed to be updated. Evaluation of each change request should always **focus on the risk assessment regarding quality of the medicinal product** and not purely on RA-submission discussions. The complete duration of a change process can be reduced without necessary regulatory submissions. GMP demands need to be met in each case, but the time-consuming regulatory submission and approval process can be shortened by generating generally-written dossiers in the first place.

In case of an approved **design space of a product,** a different strategy but with the same intention is followed: the MAH has to invest more time into development of the product resulting in this multi-factorial complex of design space. Changes that are done within in the pre-defined ranges of design space only need to be run through a change control on a formal level. Working in the approved limits of the design space defined will therefore streamline each change process. Changes within the respective design space do not need discussion about regulatory submission anymore and risk analysis can also be reduced to a minimum. Only if the MAH wants to leave the pre-defined and approved limits of design space, a regular change control process will follow including the requirement of type II variation. In those cases, the extended timeframe for regulatory approval should be regarded.

The necessity of a well-documented change control system is illustrated when looking at the duty of compilation of a **product quality review (PQR)** for a product. Changes must be included as an essential element into the PQR for investigation of failure origins, if significant deviations or trends in product quality occur.

All changes – independent from the fact they are dosser-relevant or not – need to be mentioned in a PQR. Especially those changes with a potential influence on the consistency of the respective manufacturing process or changes with possible influence on quality or stability of the final product need to be included into the PQR. Examples for seemingly minor changes with a potential impact on product quality might be changes in the environment of manufacturing, changes in qualification status or cleaning procedure of equipment used in manufacturing process.

From the Qualified Person´s point of view, a **product quality review is the most suitable tool for monitoring product quality**. Inclusion of all changes to one product into the PQR enables the QP to have a retrospective look on the effects of change requests – especially those with potential effect on quality of the product. If the QP is not directly involved into change approval and implementation process, the PQR is the only document to be signed for a product with respect to changes once a year.

The increasing complexity of a change control process shows the necessity of suitable **tracking tools** enabling the coordinating personnel to include all required information. This task can only be fulfilled with the help of **high-performance database systems** with tools enabling digital signature, auto-reminders or electronic archiving of information.

New legislation brings up the **requirement of well-trained personnel** with procedural knowlegde at both ends: the one for regulatory bodies and the one for pharmaceutical industry. Since workload is getting more and more complex, strategic thinking using working plans or similar devices is becoming increasingly important. RA personnel is facing the requirement to take responsible decisions in the course of regulatory-relevant change procedures more frequently.

3.2 Implementation Date and Implementation Plan

The new Variation Regulation and its amended guidelines have brought up a new discussion and demand that might be the most complex and most discussed topic in this connection: the **requirement to define the implementation date** in variation application forms. Generelly speaking, implementation is when the company executes the change in its own quality system.

This demand is not new and should have been covered before by each quality system. However, the request to include implementation dates into variation applications brings up the question on the exact definition of an implementation date. Different opinions about the implementation date do exist: Some define it as the date of beginning to manufacture, some as the date of batch release and finally some define it as the date of bringing the product on the market.

The Variation Regulation and its amending guidelines do not provide potential users with a concrete definition of the term “implementation”, but they state timelines for different variation types required for the implementation of changes:

- **Type IA notifications** can be implemented before submission. Depending on the importance of variation, these do & tell variations need to be notified immediately after implementation (IA_{IN} notifications) or within 12 months after implementation (IA_{Annual} notifications). Manufacturing of conformance batches are allowed as well as performing stability studies to support the IA_{IN} variation before making the immediate notification.

  In case of changes to the pharmacovigilance system (DDPS), implementation is regarded to be done once the company approves the DDPS incorporating changes.

  An update of product information is regarded as approved when the company internally approves the revised version of the document.

- **Type IB variations** always need to be submitted before implementation. These tell, wait & do submissions do not require formal approval – variation is implicitely approved after a 30 days timetable. It is the company´s decision to implement the change after 30 days or to wait until a final approval has been received by the competent authority.

- **Type II variations** always need prior approval before implementation of the change.

- **Type IB variations approved via a worksharing procedure** may be implemented upon receipt of the favourable opinion of the reference authority or EMA.

- **Type II variations approved via worksharing procedure** (and included type IB variations) may be implemented 30 days after receipt of the favourable opinion from reference authority or EMA. In case of variations to SPC, PI or label , the MAH sends national translations within 5 days after variation finalisation. Changes to SPC, PI and label are implicitely approved 30 days after submission of high-level translations to CMS, if NCA have not sent their comments on the proposed translation before.

- **Variations related to safety** may be implemented within the time frame agreed between MAH and reference authority.

- **Extension applications** always require prior approval before implementation. Such applications will be evaluated in accordance with the same procedure as for granting the initial marketing authorisation which it relates to. The extension will either be

granted a new marketing authorisation or will be included in the initial MA, to which it relates to.

- In cases of serious concerns to human/animal health or to the environment due to a pharmacovigilance, pre-clinical, safety or quality signal, interim changes to the product information might be required resulting in the need of **Urgent Safety Restrictions (USRs).** These principally can be deemed as accepted, if no objections have been raised by the relevant authority or Commission 24 hours after receipt of information. They must be implemented within a time frame agreed between the Commission or the RMS and the MAH. The outcome of such USRs needs to be communicated immediately to prescribers and users. Changes will subsequently be introduced via a corresponding variation to the MA related. Variation application must be submitted within 15 days after initiation of USR. Provisional urgent safety restrictions are normally started by the MAH, however, they may also be imposed by Commission or national competent authorities.

Procedural guideline additionally provides timelines for the implementation of changes:

- **Updates in monographs** of pharmacopoeias affecting an MA **do not require notification** to the authorities, if the new specification or **method is implemented 6 months after its publication** and the dossier references to the *current edition* of pharmacopoeia. This includes the necessity of a Regulatory Intelligence group or responsible person duly focussing on all changes made to the respective pharmacopoeias. Furthermore, the requirement of dossier updates not referring to current editions of monographs shows the necessity for generally-written dossiers. This will not redundantise the necessity of a change control system but the time and steps required for implementation of each change will be reduced significantly.

For the task of including the implementation date into each change control procedure, a **strong cooperation** between all affected parties is required. This is much easier to handle for companies focussing on a national level only. The higher the amount of affected parties and registrations, the higher the complexity and difficulty to track the information about implementation dates for each party. One complex scenario might be, if the affected product has a European licence (central, MRP or DCP) and is used for different affiliates or outlicensing partners in all European countries. Each affected site quality management needs to be included into the previously defined implementation plan (list of activities) and the subsequent change acceptance process. The **implementation plan** of each change control procedure should take into account the different timelines pre-defined by explicite or implicite approval processes of the national competent authorities. Once a regulatory

submission is successful, all partners need to be informed again and the implementation date in each country needs to be included into the change documentation.

3.3 The Importance of Regulatory Affairs in Change Management System

In course of an upcoming change, the marketing authorisation holder (in person of its RA department) respectively, should evaluate the necessity of notifications or variations. If a regulatory submission is required, the following questions should be asked in order to reach a **decision on the type of submission**:

- Does the change lead to an extension application?
- Are the criteria of a type IA variation fulfilled and if yes: is there a need of immediate notification (IA_{IN}) or possibility of notification within 12 months after implementation (do and tell = Annual Reporting).
- Is the change already listed as a type II variation?
- Is the change already listed as a type IB variation?
- Can the variation be submitted as a type IB by default? If not, submission of a type II variation or article 5 request should be done.
- Is there a need to request the CMD (or the EMA in case of central MA) for recommendation on classification of a currently unclassified variation?
- Can the submission be done on national level only (e.g. for MA transfers) or is a submission (yet) possible for nationally-authorised products?

In case of more changes to one MA running in parallel or one change requiring more than one variation, the affected RA department should define the **submission strategy** as early as possible with the final intention of reaching dossier compliance before the next release to the market. This system is getting more and more complex, if change requests are linked among each other, requiring parallel and subsequent submission.

Additionally, decision about **grouping or worksharing** should always include the **information to the regulatory bodies.** This is recommended to be done **two or three months in advance** of such submission procedures. If not included into previous discussions and list of activities before, these additional regulatory demands could be the reason for delays in implementation plan afterwards.

In case of **unforeseen variations (Article 5 of Variation Regulation)**, MAH or CA can request the CMD (or the EMA in case of central MA) for recommendation on classification of the up to now unclassified variation. Response should be delivered within 45 days and should be submitted until pre-defined submission dates.

These additional time frames potentially required to be included into a change control process and its implementation plan show the **importance of early involvement of the RA department** in pre-change discussions and the **necessity of change initiation at an early stage.**

The system of working with grouping and worksharing is easily manageable, if only one product is affected. But with an increasing amount of products and change aspects in one variation or change, the system is getting more and more complex. The MAH should take into account the possibility of submitting several changes to several products in one submission. Not only the tracking of changes is getting more and more complex, but also the tracking of submissions in the RA department.

Furthermore, the decision about the necessity of **immediate notification** or the possibility of submission within 12 months after implementation needs to be taken by the RA department in close cooperation with the quality department. These aspects show the increasing importance about the QA/RA interface in a change management system. Regulatory affairs should link these notifications directly with work needed to be done anyway, e.g. with other variations or notifications.

These discussions show the **requirement of electronic tools (e.g. databases)**, not only for tracking of changes. RA should have a tool in place ensuring the just-in-time submission of type IA variations within 12 months after implementation of the first change. Without doubt this new possibility of **annual reporting in Europe as a specific form of type IA variation grouping** is a simplification of the work at regulatory bodies, since the total amount of single variations will decrease. Pharmaceutical industry faces the problem of increasing complexity in submissions. Once a submission is affecting more than one product, archiving of dossiers is also getting complex. This is not manageable anymore without tools like document management systems and tracking tools, which again causes additional costs for the pharmaceutical industry – especially for small and medium enterprises.

3.4 Effect of new legislation on changes to national marketing authorisations

Having left behind the decision date of 20 January 2011, it will be visible how far the aim of harmonisation process of European Variation system has proceeded. National competent authorities need to decide on the potential implementation of the Variation Regulation also for their purely national authorised products. This decision is elementary, especially for these countries that tried to stick to their old system, e.g. the §29 of German Drug Law (AMG). This system has been proven to be very robust, since tell and do submissions were possible for many change aspects and only few changes were needed to be run in tell, wait & do submissions (latency of 3 months) or even new applications.

The compromise of establishing special rules for older products with a registration date before 01.01.1998 would be an advantage for these products since from an MAH´s point of view national applications according §29 AMG are much easier to handle than variation applications: less paperwork is required since many change aspects can be combined in one submission without the need of taking care that grouping or worksharing is possible or that a variation needs to be submitted as type IA, IB, II variations or even extension applications.

The clear disadvantage of having two systems (the one for products approved before and the others approved after 1998) running in parallel is the higher complexity regarding regulatory strategy and regulatory submission during change activities. Every department in the loop of change implementation should know, what kind of licence is affected and thus what kind of regulatory change strategy has to be followed: the “national way” or the submission according to new Variation Regulation 1234/2008.

Further national specialities do exist: National competent authorities are using the “new system” but with different timelines than mentioned in Procedural Guideline.

These discussions show that a full harmonisation of the variation systems in Europe has not been achieved completely. Regulatory departments and quality management need to know that there are further differences in the European countries that need to be taken into account for each regulatory relevant change. Different timelines, documentation to be supplied or even cost issues might need to be included into the change disucssion process, before a decision about the possible implementation timeframe can be taken.

3.5 First experience with the new variation system

First experience from CMD has shown that applicants prefer to submit **variations of non-classified aspects** as type II variation, rather than the intended way via type IB variation showing that companies want to avoid discussions with the authorities in pre-course.

Furthermore, it is considered to be an additional barrier that only those change aspects can be **grouped** that are consequential or related. Possibility of diverging from this rule after approval of EMA or reference authority is currently under discussion.

In addition furthermore, it is currently being discussed, if a type IA notification with **insufficient or deficient documentation** need to be submitted again with the consequence of additional regulatory fees or if amendments to the first submission is allowed.

For **worksharing procedures,** authorities do only have little experience up to now, especially due to of the 3-months-requesting period before submission. Applicants need to include a justification for the upcoming worksharing procedure. If any authority rises PSRPH in course of a worksharing procedure, the applicant can withdraw the variation before closure of the worksharing procedure with the intention to avoid a referral procedure.

New aspects of the Variation Regulation were previously intended to facilitate the variation system. Pharmaceutical industry complains about the **more bureaucratic system** leading to extra work load and financial expenses.

4 Conclusion and Outlook

Variation Regulation (1234/2008/EC) has had a significant impact on the processes of pharmaceutical industry, national competent authorities / EMA and for CMD. With regard to the applicant, a simplification of procedures was intended to be reached taking into account the different possibilities of combination of single changes. The national competent authorities are facing new challenges regarding handling of grouping, annual reporting and worksharing. Finally, the coordination groups (CMDh and CMDv) have taken over additional tasks resulting from Article 5 of Variation Regulation: they are now responsible for recommendations, coordinating worksharing procedures as well as CMD referrals for variations, grouping and worksharing.

In this context it has to be summarised that national special rules with respect to regulatory demands lead to more complexity in Regulatory Affairs and also in Change Management: the more special rules exist, the more requirements for implementation and closure of a change have to be taken into account. The intention of the Variation Regulation to simplify the variation system was not fully achieved.

Since not all of the European Member States have decided to use the rules from the Variation Regulation and its amending guidelines, a final statement about the profit of these rules can only be given after January 2011 (deadline of Directive 2009/53/EC). Once the member states have decided upon the application of the Variation Regulation to all of their purely national marketing authorisations or to only those licensed after 01 January 1998, companies need to adapt their processes to the national particularities.

Transposition of Variation Regulation to national law also needs to be taken into account. Beside the discussion about Directive 2009/53/EC, different countries are also following the rules of Regulation 1234/2008, but with different timelines for variations. This case also needs to be taken into account for changes affecting countries with different timetables.

In case of Germany, the decision about §29 of German Drug Law needs to be made. If the national system will be only used for products licensed after 01 January 1998, Germany will have two completely different variation systems running in parallel: on one hand the previous, less bureaucratic and more flexible system of §29 AMG and on the other hand the new system of the Variation Regulation. In case of two differently running variation systems, a change control system also needs to take these special rules into account. Even though the quality demands for each change can be regarded as equivalent, the effect on the timetable for implementation of a change can be significantly different, if a submission can be run via §29 AMG (tell and do submission not requiring authorised approval for

implementation; not valid for subparagraph 2a) compared with a type II variation requiring approval for implementation.

Taking all this together, the importance of Regulatory Affairs in change management system has increased further with the Variation Regulation. RA Managers always need to give their input in change requests, especially in those of regulatory relevance. RA needs to decide on the regulatory strategy directly influencing the implementation strategy of Quality Assurance as responsible department of change control requests.

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