2 years Variation Regulation: A retrospective critical assessment from the industrial perspective

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

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Bonn 2012

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List of Abbreviations

AMG	Arzneimittelgesetz
ASMF	Active Substance Master File
BASG	Bundesamtes für Sicherheit im Gesundheitswesen
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BPI	Bundesverband der Pharmazeutischen Industrie
CA	Competent Authority
CEP	Certificate of Suitability to the Monographs of the European Pharmacopoeia
CMD	Coordination group for Mutual recognition and Decentralized procedure
CMDh	Coordination group for Mutual recognition and Decentralized procedure (human)
CP	Centralised Procedure
DCP	Decentralised Procedure
DDPS	Detailed Description of the Pharmacovigilance System
EBE	European Biopharmaceutical Enterprises
EC	European Commission
eCTD	Electronic Common Technical Document
EFPIA	European Federation of Pharmaceutical Industries and Associations
EC	European Commission
EGA	European Generic Medicines Association
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
EVM	European Vaccine Manufacturers
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MA	Marketing authorization
MAH	Marketing Authorization Holder
MHRA	Medicines and Healthcare products Regulatory Agency
MRP	Mutual Recognition Procedure
MS	Member State(s)
NeeS	Non-eCTD electronic Submissions
PhVWP	Pharmacovigilance Working Party
QC	Quality Control
Q/A	Questions and Answers
QC	Quality Control
QP	Qualified Person
RMS	Reference Member State
SmPC	Summary of product characteristics
UK	United Kingdom
US	United States

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1. Introduction:

A marketing authorisation dossier shall demonstrate the quality, safety, efficacy and a positive benefit-risk-ratio of the respective medicinal product. Throughout the life-cycle of a medicinal product, the dossier is subject to a continuous change. The documentation is amended in order to be adjusted to the state of art in science, technology and knowledge. Other trigger for an amendment may be a growing experience with the medicinal product or modified market needs.[1]

Any variation to the dossier, meaning addition, replacement or deletion of information or documents triggers a variation. In the EU, the legal base for the examination of variations is provided by Commission Regulation (EC) No 1234/2008 (hereafter also called Variation Regulation).

1.1 Evolution of the Variation Regulation

Commission Regulations (EC) No 541/95 and (EC) No 542/95

On 1st of January 1995, the Centralised Procedure (CP) and the Mutual Recognition Procedure (MRP) were introduced, giving the opportunity to receive a marketing authorisation (MA) for a medicinal product in all or several Member States (MS) in the EU. This required also new common rules for variations in the post-marketing phase, in order to keep these MAs harmonised. This resulted in the first Commission Regulations concerning the examination of variations, (EC) No 541/95 for MAs authorised via MRP and (EC) No 542/95 for MAs authorised via CP, both dated 10th of March, 1995.[2]

These first regulations for variations only defined a list of minor variations (Type IA) in its Annex 1 and changes to a marketing authorisation leading to a new application in its Annex 2. All not listed variations were categorised as major variations (Type II). The designated timelines were 30 days with an implicit approval for Type IA variations and 60 days for Type II variations requiring an explicit approval.[3]

Commission Regulations (EC) No 1084/2003 and (EC) No 1085/2003

In order to simplify the variation procedure, the above mentioned initial variation regulations were repealed and replaced by Commission Regulations (EC) No 1084/2003 for MRP and (EC) No 1085/2003 for CP, both dated 3rd of June 2003.[4]

1 Study documentation, MDRA-13, Modul 1
2 Commission Regulations (EC) No 541/95 and (EC) No 542/95
3 Commission Regulations (EC) No 541/95 and (EC) No 542/95, Articles 3, 5, 7
4 Commission Regulations (EC) No 1084/2003 and (EC) No 1085/2003

The general principles of the former Regulations (EC) No 541/95 and (EC) No 542/95 were maintained but adjusted. An additional procedure for minor variations was introduced resulting in the Type IA and Type IB categorization of variations. For Type IA variation procedure, the concept of a simple administrative validation concept was introduced, whereby the Type IB variations were now subjected to the previous concept for Type IA (implicit approval after 30 days).[5] In addition, the timeline for a Type II variation was designed more flexible by introducing a 90 days timeline, e.g. for change in indications, and the opportunity to reduce the timeline in urgent cases.[6] Two additional articles, "Human influenza vaccines" (Article 7) and "Pandemic situation with respect to human diseases" (Article 8) were also introduced.

Commission Regulation (EC) 1234/2008

On 1st of January 2009 the Commission Regulation (EC) No 1234/2008 entered into force, replacing the former Commission Regulations 1084/2003 and 1085/2003. Since 1st of January 2010, the new Variation Regulation is applicable for all MAs registered via CP, MRP or the Decentralised Procedure (DCP). So for the first time, all European procedures are now covered by the same regulation with regard to post-authorisation variations.
Commission Regulation (EC) 1234/2008 was introduced "in order to establish a simpler, clearer and more flexible legal framework, while guaranteeing the same level of public and animal health protection."[7]
Type IA variations are now defined as "Do and tell" procedures and are split in two sub-categories, including Type IA_{IN} for variations requiring immediate approval and Type IA for variations that can be submitted via an Annual Report within 12 months after the implementation of the variation.[8]

In contrast to Regulations (EC) No 1084/2003 and (EC) No 1085/2003, wherein Type IA and Type IB variations were listed in the Annex, now IA variations are classified together with Type II variations. As a consequence, unlisted changes are now categorized as Type IB variations instead of Type II variations.[9]

5 Commission Regulations (EC) No 1084/2003 and (EC) No 1085/2003, Articles 4, 5
6 Commission Regulations (EC) No 1084/2003 and (EC) No 1085/2003, Articles 6
[7] Commission Regulation (EC) No 1234/2008
[8] Commission Regulation (EC) No 1234/2008, Article 8
[9] Commission Regulation (EC) No 1234/2008, Article 3

In addition, the possibility of submitting several variations to together in one application (Grouping and Worksharing) was introduced.[10]

In order to simplify updates to the categorisation of variations, the classification of variations was removed from the Regulation and is now part of the guidelines referred to in point (a) of Article 4(1) of Commission Regulation (EC) 1234/2008 - "Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products" (hereafter referred to as Classification Guideline).[11]

Directive 2009/53/EC

As only medicinal products authorised via CP, MRP and DCP are in the scope of Commission Regulation (EC) 1234/2008, purely national MAs are still subject to national rules. In order to promote further harmonisation within Europe, Directive 2009/53/EC of 18 June 2009 was put into force, amending Directives 2001/82/EC and 2001/83/EC and extending the Variation Regulation 1234/2008 to only nationally authorised products.[12]

Thus after the implementation of Directive 2009/53/EC and the amending Directives 2001/82/EC and 2001/83/EC into national law, the Variation Regulation will also be applicable for purely national MAs. Therefore, Variation Regulation 1234/2008 will be updated again to include a new chapter for national variations.

Thereby, all MAs for human or animal medicinal products will be covered by the same Variation Regulation, independent from the registration procedure.

1.2 Retrospective assessment of Commission Regulation (EC) No 1234/2008

As mentioned above, Commission Regulation (EC) No 1234/2008 is applicable since 01st of January 2010.

The harmonisation of the variation procedures within Europe covering CP, MRP and DCP is one of the most essential objectives of Regulation 1234/2008. Another important purpose of the revised Variation Regulation is the decrease of workload of the competent authorities (CA) and the industry by designing the "legal framework simpler, clearer and more flexible." Furthermore, reducing the administrative burden and the adaptation of the variations to ICH concepts is another objective.[13]

[10] Commission Regulation (EC) No 1234/2008, Articles 7, 20
[11] Classification Guideline
[12] Directive 2009/53/EC
[13] Commission Regulation (EC) No 1234/2008

The following key features of the Variation Regulation that were introduced mostly affect the Regulatory Affairs routine:

- Type IA: “Do and tell” and Annual Report
- Grouping of variations
- Worksharing
- Type IB by default

In this master thesis, a retrospective assessment regarding the applicability of the Commission Regulation (EC) 1234/2008 is carried out two and a half years after it came into effect.
With this master it is intended to show to what extent the different above mentioned tools were adopted by the industry, what kind of advantages and challenges are associated with these innovations and their impact on workload, strategic planning and costs.
Finally, the master thesis discusses possible areas for improvement and provides an outlook on the challenges potentially occurring once the Variation Regulation will also apply for purely national MAs.

1.3 Survey on Commission Regulation (EC) No. 1234/2008

A survey on the Commission Regulation (EC) No. 1234/2008 was carried out in order to assess the own practical experiences and opinions.
As only feedback from 23 participants was received, a real statistical evaluation is not feasible. Nevertheless, the results are considered as relevant and are taken into account, as feedback was received from 18 different companies, including several generic companies, originators, regulatory consultants and also one company producing veterinary medicinal products.
The survey gathered feedback on the utilisation and the practicability of the Commission Regulation (EC) 1234/2008, focussing on the above mentioned innovations, other special cases and the effect on costs for variations.
The level of agreement to several statements to Commission Regulation (EC) No. 1234/2008 was requested. The options for answering ranged from “5” meaning “I fully agree” to “1” meaning “I do not agree”. In some cases, also the extent of usage was requested with the following optional choices: 5: routinely, 4: commonly, 3: uncommonly 2: rarely, 1: no experience yet.
Several particularly meaningful results are included in the master thesis. A tabulation of the survey outcome is attached in Annex 2 of this thesis.

2. Type IA - “Do and tell”

In the former Commission Regulations 1084/2003 and 1085/2003, Type IA notifications were defined as “Tell and do”. Thus the MAH needed to submit the variation to the CA prior to the implementation of the change. With the update of the Variation Regulation, Type IA notifications are now subject to a “Do and tell” procedure and can therefore be implemented prior to the notification to the relevant authorities.

According to the new Variation Regulation, the notification regarding a minor variation shall be submitted within 12 months following the implementation of the variation (Type IA) or immediately after the implementation when immediate notification is required for continuous supervision (Type IA_{IN}).[14]

2.1 Advantages

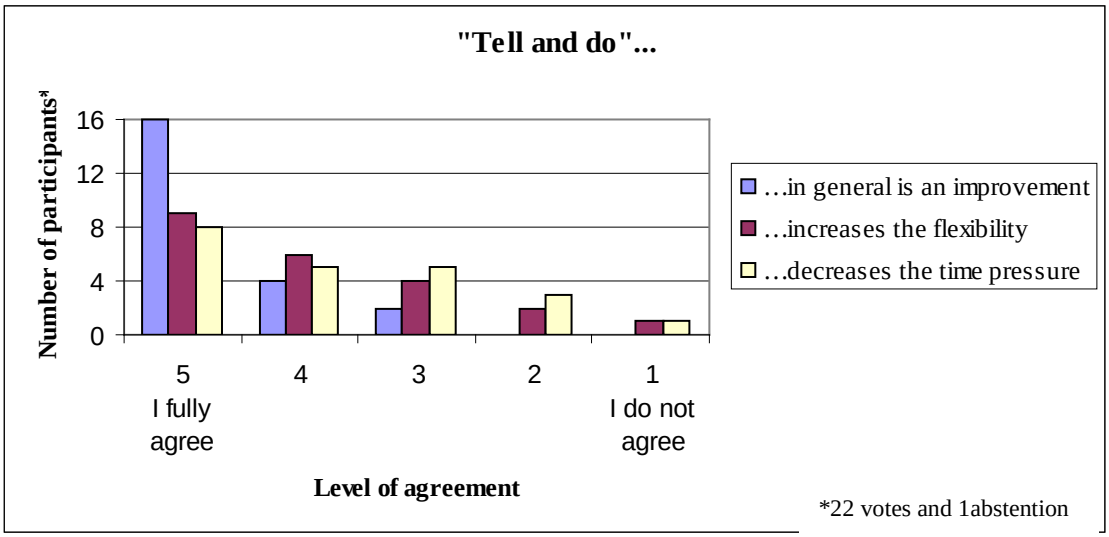
This innovation was highly appreciated by the industry as the notification of Type IA variations to the CAs was often the time-limiting step, prolonging the timelines for implementation. This boosted the time-pressure in the Regulatory Affairs Departments, as submission needed to be carried out promptly in order to avoid a delayed implementation. With the innovation of “Do and tell”, this time-pressure has been decreased as implementation is now possible prior to the notification. Another effect of the “Do and tell” procedure is that the flexibility in Regulatory Affairs Departments has significantly increased. High peaks of workload can be cushioned by re-scheduling the submission date where possible, without preventing the respective implementation of the change in time.

Survey outcome

As Figure 1 shows, nearly all participants of the survey share the view that the introduction of the “Do and tell” procedure is an improvement and entails the above mentioned advantages.

[14] Commission Regulation (EC) No 1234/2008, Article 8

Figure 1: Survey outcome - Level of agreement on various statements regarding the “Do and tell” procedure



Source: Survey on the Commission Regulation (EC) No 1234/2008, attached in Annex 2

2.2 Challenges

Nonetheless, there are also several challenges linked with “Do and tell” variations.

Fixing the implementation date

One of the biggest challenges for using the “Do and tell” procedure is to fix the respective implementation date of a change. Even though the definition of “implementation date for Type IA variations” is given in the “Q/A List for the submission of variations according to Commission Regulation (EC) 1234/2008” published by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh Q&A-List), this is still an issue, which often requires further discussion.

For example, the following definition for implementation of Type IA variations is given in the Q&A-List:

“For quality changes, implementation is when the Company makes the change in its own Quality System. This interpretation allows companies to manufacture conformance batches and generate any needed stability studies to support a Type IA$_{IN}$ variation before making an immediate notification because the change will not be made in their own Quality System until these data are available.”[15]

[15] CMDh Q/A List, Question 5.2

This definition is, in spite of the added explanation, quite imprecise and still allows room for discussion. Thus, a clearly defined procedure for determining the implementation date of a change/variation must be in place and monitored regularly.

Tracking of implementation / submission dates

The gain in flexibility by the Variation Regulation is not only an advantage but also represents a challenge, as a more precise tracking of the implementation and submission dates is required now. In order to maintain regulatory compliance, it is essential to carefully monitor the timelines. This requires new processes and is only possible with a good cooperation between the Regulatory Affairs Department and other departments within the company such as Change Control or Quality Control (QC).

Interpretation of “Immediate notification”

Type IA_{IN} variations must be notified immediately after implementation. As there is no exact explanation regarding the timelines, the interpretation of “immediate notification” still varies within the authorities and the pharmaceutical companies. So it is advisable to define a clear and consistent time period for immediate notification within the company, that will also be accepted by the agencies (e.g. notification two weeks after implementation at the latest), in order to avoid requests or invalidation. This may also have the positive effect that based on the implementation date, the latest possible submission date for IA_{IN} variations can be fixed easily and consistently.

This simplifies the tracking of related variations and thereby contributes to regulatory compliance.

National MAs are not yet in the scope of the Variation Regulation

As purely national MAs are not yet in the scope of the Variation Regulation, the “Do and tell” procedure is not feasible for national MAs. For example in Germany, these variations are still subject to a “Tell and do” procedure. However, there are also countries that already apply the Variation Regulation also to their purely national MAs such as UK.

This can cause difficulties either with a consistent implementation date across Europe or with a consistent valid dossier. A problem occurs especially in the case that different purely national MAs are based on the same dossier, e.g. a national duplicate of a DCP.

In that case, one option of the MAH is to interrupt the harmonisation of the common dossier until pending variations are valid for all related MAs. As a consequence, the MAH needs to maintain different dossiers in the meantime, which might be a complex task, depending on the number of dossiers. This again might increase the workload.

The other alternative is to define different implementation dates for the various MAs. This possibility should be considered carefully, as first of all, implementation dates should not be fixed arbitrary, and second, this procedure will require an even more careful tracking.
Nevertheless, this issue will be solved as soon as all purely national MAs will fall under the scope of the same EU-wide Variation Regulation, which will be in the near future.

No opportunity for “Tell and do”

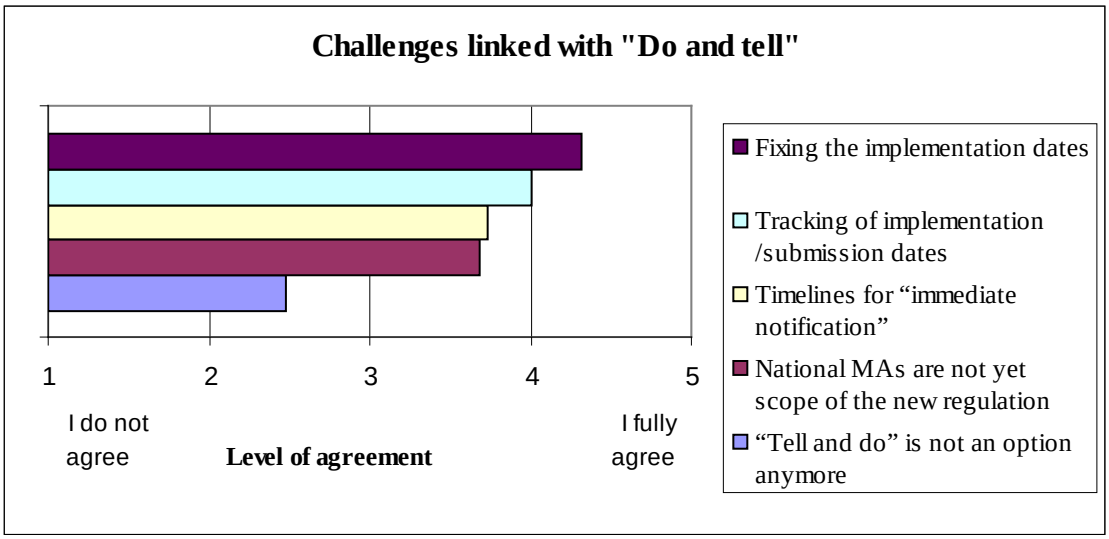
The Type IA procedure of the new Variation Regulation does not include the opportunity to submit Type IA variations prior to the implementation date. A Type IA change may only be submitted with an implementation date in the future in case it is dependent on the outcome of other changes in a grouped application (e.g. IA variation grouped with a Type IB/II variation)[16].
The opportunity of “Tell and do” would partially solve the above mentioned difficulties regarding the purely national MAs, as a common implementation date for European and national MAs could be fixed.
In addition, it would also increase the flexibility in the Regulatory Affairs Department as upcoming Type IA variations could be submitted in times of low workload. Furthermore, it would be favourable, if such variations could be included in a grouped Type IA notification independent of the implementation date.

Survey outcome

Figure 2 points out the mean values of 22 participants (1 abstention), regarding their opinion on the different challenges linked with “Do and tell”. As can be seen, the survey confirmed that, mainly the fixing and tracking of implementation and submission dates including the timelines for immediate notification are considered as challenges linked with “Do and tell”, followed by the fact that national MAs are not yet in the scope of the new Variation Regulation.

[16] CMDh Q/A List, Question 5.3

Figure 2: Survey outcome - Level of agreement on statements regarding the challenges linked with the “Do and tell” procedure (Mean values)



Source: Survey on the Commission Regulation (EC) No 1234/2008, attached in Annex 2

2.3 Summary

The introduction of the “Do and tell” procedure has diverse positive effects. The flexibility in the Regulatory Affaires Department is increased as submissions can be adapted to the current workload. In addition, for minor variations, the submission to the CAs, previously the final step in the implementation procedure, is not longer the time limiting factor. This decreases the time-pressure in the Regulatory Affairs Department. Regarding the whole company, an implementation prior to the submission may also have a positive effect on the ability to supply.

Nevertheless, taking into consideration also the new challenges evolving from the implementation of the new Variation Regulation, the “Do and tell” procedure does not simplify the regulatory work. However, in case of an intensive tracking of variations and a consequent determination of timelines and implementation dates, the above mentioned challenges can be met.

3. Type IA – Annual Report

As mentioned above, the notification for a Type IA variation can be submitted within 12 months following the implementation of the variation, as so-called Annual Report.[17]

The Annual Report can be seen as the extensive option of the "Do and tell" procedure offering the pharmaceutical companies the opportunity to submit a list of Type IA variations, which do not require immediate notification within 12 months following the implementation of the first involved Type IA variation.

3.1 Advantages

The Annual Report offers an even higher level of flexibility compared to the "Do and tell" procedure, as the submission date can be chosen by the MAH e.g. depending on the workload, as long as the 12 months deadline is kept.

Another advantage of the Annual Report is, that in case the submission is postponed for several months, further data may be available (e.g. the validation report instead of the required validation protocol). This may prevent an additional variation and thus additional workload and costs. Since, in case this data is supposed to be included in the dossier later, the inclusion normally requires a separate variation.

Survey outcome

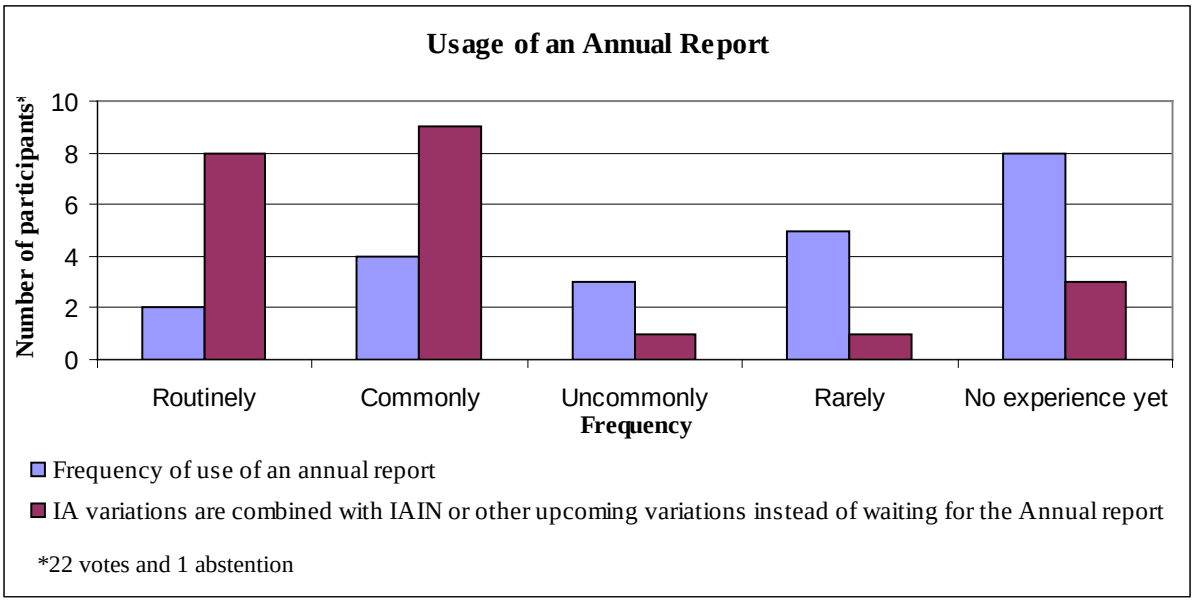
The outcome of the conducted survey on the Variation Regulation gives evidence that the Annual Report is seen as an improvement. The mean level of agreement of 22 participants (1 abstention) on this particular statement is very high (4.4, whereas 5 means "I fully agree" and 1 means "I do not agree"). For the exact result, please refer to the Survey Summary, attached in Annex 2.

3.2 Usage of an Annual Report

Even though the Annual Report is regarded as improvement by most of the survey participants, a real annual report is apparently not submitted by MAHs very often. Only 6 participants of the survey declared that an Annual Report is used routinely or commonly, whereas 8 participants do not have any experience with an Annual Report yet. Please refer to Figure 3.

[17] Commission Regulation (EC) No 1234/2008

Figure 3: Survey outcome - Frequency of the Annual Report utilisation



Source: Survey on the Commission Regulation (EC) No 1234/2008, attached in Annex 2

Flexible approach to combine Type IA variations with a Type IA_{IN} variation

The hesitant use of the Annual Report may be connected with the possibility of combining Type IA variations with Type IA_{IN} or other upcoming variations (please refer to chapter 4. Grouping). The extent of usage of this option is also included in Figure 3.

Since the submission of Type IA notifications as Annual Report is not mandatory, it is up to the applicant if and when to submit an Annual Report[18]. 84 Type IA variations and 42 Type IA_{IN} variations are classified in the Classification Guideline.[19] Thus, one third of all minor Type IA changes require immediate notification. With the Variation Regulation the MAH is offered the possibility "to include a Type IA variation in the submission of a Type IA_{IN} variation, or with another upcoming variation, rather than waiting to include it in an annual reporting."[20]

If for a Type IA_{IN} variation the dossier must be updated and an application form must be completed anyway, this is a good chance to include all open Type IA variations in this notification. In consequence, the respective dossier is aligned to the real situation earlier, without need of an extra submission. Thus, using this opportunity may have a positive impact on the workload.

[18] CMDh Q/A-List, Question 4.4
[19] Classification Guideline
[20] CMDh Best Practice Guides for the Submission and Processing of Variations in the MRP, Rev. 16 (Chapter 3)

For these reasons, the option of combining Type IA variations with other upcoming variations is a commonly used alternative to the Annual Report.

3.3 Challenges

The different challenges linked with an Annual Report may also be the reason for its hesitant use.

Intensive tracking

An even more accurate tracking of the implementation dates and related latest possible submission dates is required for an annual reporting of Type IA variations than for "Do and tell" procedures immediately reported.

Most changes affecting a MA are minor changes, requiring a Type IA variation. Hereby a high volume of Type IA variations accumulate within 12 months. As a consequence, the preparation of the Annual Report is very time-intensive and sufficient capacities must be available just before the expiry of the 12 months period.

Especially for generic companies, with a huge amount of MAs, it is quite difficult to keep all open variations in view and guarantee a timely submission of the Annual Report.

This is only possible with a robust and comprehensive database, a consistently monitoring change control system and a reliable document management system.

GMP documents are not in line with the dossier for an unpredictable period of time

A close collaboration between the different departments in the company is also essential.

In case the Type IA variation are chosen to be reported by means of an Annual Report, the valid dossier does not comply with the related GMP documents for an undefined period of time – however, not longer than a maximum of one year. Nonetheless, departments like QC, especially the responsible Qualified Person, must strongly rely on the correct submission planning of the Regulatory Affairs Department. Otherwise frequent queries are unavoidable.

Potential rejection of variations included in the Annual Report

As any Type IA variation is implemented prior to notification, a rejection of a Type IA variation may have an impact on already marketed product. Although this effect is also given by an immediate notification, the risk is even increased by annual reporting. The more time passes between implementation and notification, the more critical may be the effect, particularly as the amount of already changed product on the market potentially increases.

Of course, the extent of the impact regarding a potential variation rejection depends on the respective reasons.

If a variation is rejected due to incomplete submission or administrative errors, submission can simply be repeated. In this case, no impact on already marketed products is expected. Nevertheless, in order to guarantee permanent regulatory compliance, it should be considered to not exhaust the whole 12 months period, but to integrate a time buffer for a repeated submission.

Although, Type IA variations are not completely assessed, but only validated, variations can be rejected with regards to content (e.g. variation no B.II.d.1 d) - Deletion of non-significant specification parameter)[21], if the agency does not agree with the MAH´s opinion.

This kind of rejection can really have a critical impact on the marketed product. In those cases, it is the responsibility of the MAH to perform a risk assessment and to determine further actions.

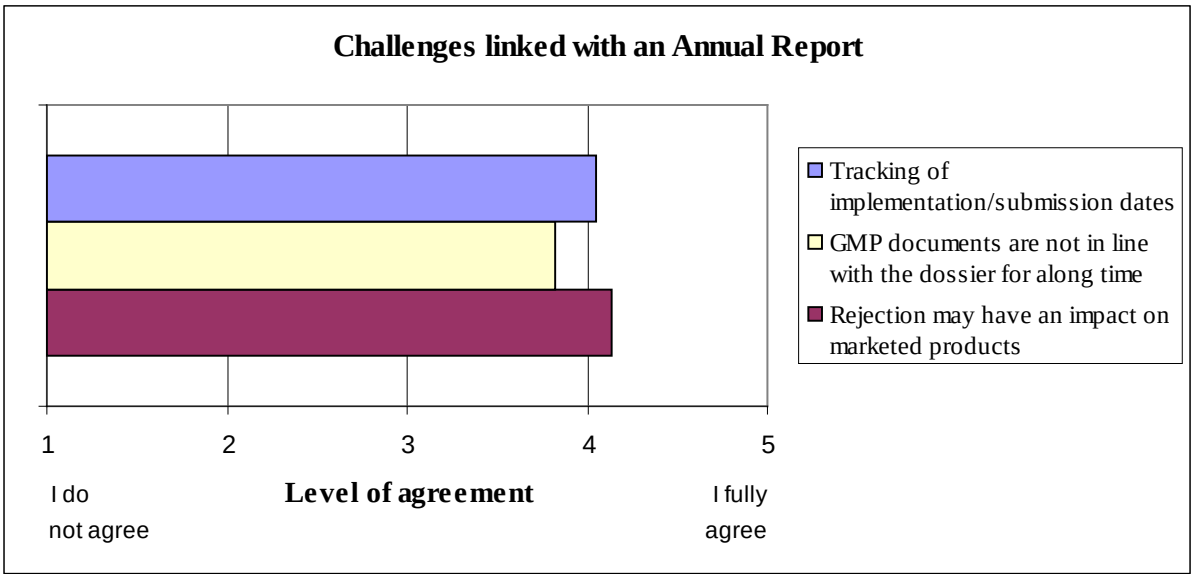
In conclusion, the risk of a retrospective rejection can not be avoided in a “Do and tell” procedure. Therefore, the MAH should carefully consider what kind of changes can be submitted via an Annual Report and what kind of changes should preferably be submitted timely. With a consequent previous assessment, critical impacts on already marketed products can thereby be limited.

Survey outcome

The survey confirmed that the use of an Annual Report is linked with the above mentioned challenges. Figure 4 points out the mean values of 22 participants (1 abstention), regarding their opinion on the different challenges linked with an Annual Report.

[21] Classification Guideline

Figure 4: Survey outcome - Level of agreement on statements regarding the challenges linked with an Annual Report (Mean values)



Source: Survey on the Commission Regulation (EC) No 1234/2008, attached in Annex 2

3.4 Summary

The Annual Report enhances the flexibility but also the challenges of the "Do and tell" procedure even more. Therefore, it must be carefully considered whether an Annual Report is useful and feasible for the related variation. In many cases, a partial Annual Report (e.g. collecting the IA variations until another variation is coming up) may be more appropriate.

However, the option to submit an Annual Report should be kept, as for several MAs (e.g. with only a few required minor variations per year), it might be useful.

4. Grouping

In the former Commission Regulations 1084/2003 and 1085/2003 it was defined that an application shall only concern one variation. Therefore, in case several variations were intended to be submitted, a separate application was required for each variation[22]. In contrast, Commission Regulation (EC) 1234/2008 now allows the reporting of several changes in one single application, the so-called Grouping.[23] In case the same MAH applies for several variations, Grouping is possible in the following circumstances:

- Type IA/IA_{IN} variations: Several changes to one MA
- Type IA/IA_{IN} variations: One change or several identical changes to several MAs
- Type IA/IA_{IN}/IB/II variations or extensions: as listed in Annex III of the Variation Regulation

In addition or in case of uncertainty, the MAH can request the permission for Grouping from the Reference Member State (RMS).[24]

4.1 Advantages

Several advantages are associated with this innovation.

For the pharmaceutical industry, Grouping has a very positive impact on the workload. The amount of application forms that are required to be completed is decreased and consequentially less inclusion of administrative data and less paper copies are required.

As for Groupings, excluding Type IA Groupings, the concerned variations should always be consequential and/or related, combining of these variations simplifies the preparation and the review of all involved variations for both, the industry and the authorities.

Especially the combination of “Do and tell”, Annual Report and Grouping is useful as it offers the pharmaceutical industry the opportunity to collect variations and finally submit them within one application.

Under several circumstances, the positive impact of Grouping on the regulatory workload is particularly distinctive. In the case several related changes need to be submitted and implemented at the same time point, e.g. a complete new supply change with consequential changes, the Grouping of all required variations guarantees a common assessment and a common timeline. Grouping is also very favourable for a change, requiring a Type IA variation that affects many different MAs, such as a change to an existing Detailed Description of the Pharmacovigilance System (DDPS).

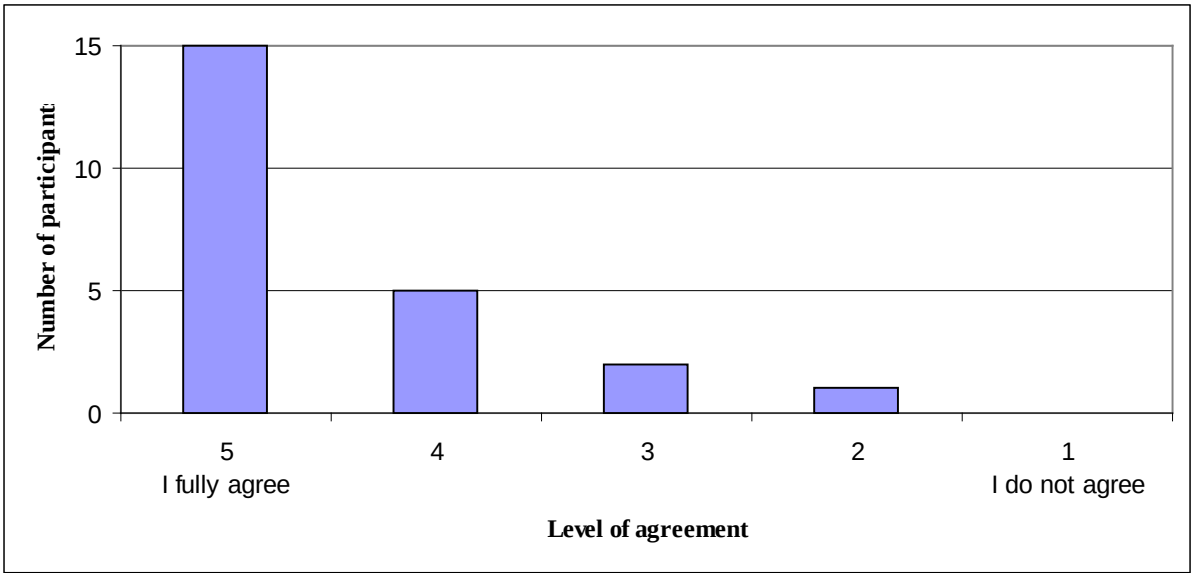
[22] Commission Regulations (EC) No 1084/2003 and (EC) No 1085/2003, sections 4, 5, 6
[23] Commission Regulation (EC) No 1234/2008, Article 7
[24] CMDh Best Practice Guides for the Submission and Processing of Variations in the MRP, Rev. 16 (Chapter 6)

In several cases, Grouping can also trigger a positive effect regarding the budget of Regulatory Affairs Departments. Some Member States e.g. UK, introduced a fee for Groupings, what may lead to a decrease of variation costs.[25]

Survey outcome

This positive view on the introduction of Grouping was confirmed by the survey. 19 of 23 participants fully or mostly agree with the statement that Grouping is an improvement (please refer to Figure 5).

Figure 5: Survey outcome – Level of agreement on the statement: Grouping in general is an improvement



Source: Survey on the Commission Regulation (EC) No 1234/2008, attached in Annex 2

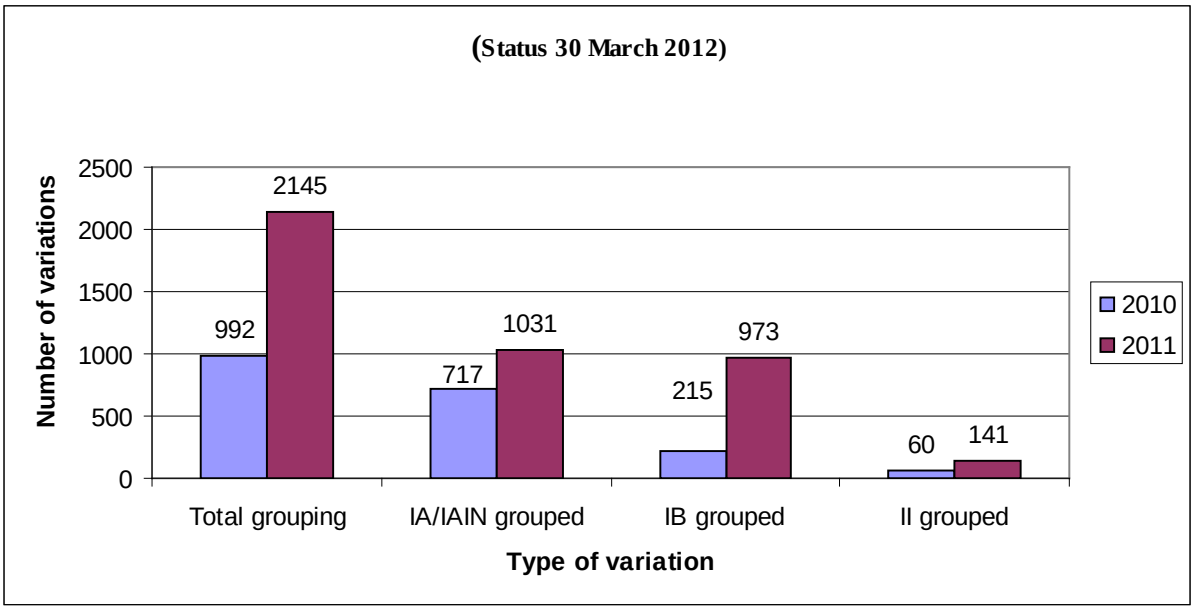
4.2 Usage and Progress of Grouping

Due to the simplification and reduction of workload, the possibility of Grouping was adopted by the industry very quickly. 51% of variations were received in grouped applications/notifications already in 2010 at the European Medicines Agency (EMA). This percentage continuously increased to 61% in 2011 and 63% up to April 2012.[26]

The same trend, shown in Figure 6, is also seen at the "Bundesinstitut für Arzneimittel und Medizinprodukte" (BfArM), where the number of grouped variations has more than doubled from 2010 to 2011.

[25] MHRA, Fees for licence variations applications
[26] EMA - Monthly statistics report: April 2012 (Not included in the percentage are multi product IA groups)

Figure 6: Received Groupings at BfArM (as RMS)



Source: BfArM letter, attached in Annex 1

Regarding the distribution by variation type, Figure 6 shows that Type IA and Type IA_{IN} variations are mostly included in a Grouping. This has various reasons. On the one hand, the total amount of Type IA / IA_{IN} variations is much higher than for Type IB or Type II variations and on the other hand, Type IA / IA_{IN} variations do not have to be related or consequential, since they can be grouped in any case.

Type IB and Type II variations can be grouped either in case the conditions of Annex III of Commission Regulation (EC) 1234/2008 are fulfilled or once a permission of the Reference Member State (RMS) is given.[27] The procedure to ask for this permission varies among the agencies. This may have led to uncertainties, regarding the applicability of Grouping. Thus, grouping of Type IB and Type II variations was only used hesitantly at the beginning. But, as Figure 6 gives evidence, the number of Groupings for these variation types increased significantly in 2011, proving that the applicants as well as the agencies got more familiar with their proceeding.

The Coordination group for Mutual recognition and Decentralized procedure (human) (CMDh) is publishing a comprehensive List on "Examples for acceptable and not acceptable groupings for MRP/DCP products" which is continuously updated.

[27] Commission Regulation (EC) No 1234/2008, Article 7

Thus more and more examples are published. Up to today, information on various frequently used variations is included.[28]
This list is very helpful for the applicants, as it provides further clarification concerning acceptable or unacceptable Groupings and thus reduces inquiries addressed to the authorities. This statement is underlined by the outcome of the survey regarding this particular question. Please refer to Annex 2.

As mentioned above, it is also possible for Type IA/IA_{IN} variations to group the same change over several MAs. Nonetheless, it is even possible to group several identical changes to several MAs, so-called "Supergroups", in a single variation application.
At the EMA, only 31 multi-product groups were received in 2010. Although this number also increased to 99 in 2011[29], the type of Grouping is not nearly as commonly used as the Grouping of changes for one MA.
A probable cause for that is, that the procedure for multi-product Grouping is more complicated and time consuming. Reason for this is that, among others, prior to submission, a variation procedure number must be requested from the RMS and the maintenance of the different affected dossiers is sophisticated.
Thus, Grouping across MAs is not as simple as Grouping within one MA, but requires proactive planning. Anyhow, it is suitable if many MAs are affected by a change.

In case a variation affects MAs with different RMS, the procedure is even more complex, and special rules must be considered prior to the submission of such an application (e.g. the applicant must choose a "Lead-RMS" and request its acceptance to act as such.) As the whole procedure is quite complicated, not only for the applicant but also for the CAs, it was strongly recommended for a long time, to prepare Groupings of variations only for MAs with the same RMS in order to simplify the handling of such grouped applications.[30]
The CMDh started a 6 months pilot phase in August 2011 for allowing the submission of grouped applications. The 6 months pilot phase was successfully completed. Nevertheless, due to its complexity, this procedure is still "restricted to purely administrative changes and other changes of Type IA/IA_{IN} that do not contain any product specific information."[31]

[28] Examples for acceptable and not acceptable Groupings for MRP/DCP products
[29] EMA - Monthly statistics report: April 2012
[30] CMDh Best Practice Guides for the Submission and Processing of Variations in the MRP, Rev. 14 (Chapter 6)
[31] CMDh Best Practice Guides for the Submission and Processing of Variations in the MRP, Rev. 16 (Chapter 6)

4.3 Challenges

Regardless of the advantages and the frequent use, challenges are also associated with Grouping.

Request for Grouping-permission

For Type IB/II Groupings, the request for Grouping-permission takes additional time. And as no timeline is defined for a Grouping-permission, the time-period until permission depends on the CA and is not predictable. This might cause difficulties, since time is always a critical factor in Regulatory Affairs Departments.

Submitting variations as a grouped application without prior permission, is mostly no real alternative as it may lead to invalidation. Thus, Grouping is not appropriate for time-critical projects with no extra time as buffer.

In addition and as already mentioned, the procedure to ask for a Grouping-permission varies among the agencies meaning that applicants must familiarise themselves with the different procedures within different countries.

Maintenance of dossiers

The maintenance of marketing authorisation dossiers, especially for NeeS or eCTD submissions, is also a major challenge linked with Grouping. As the version number of a dossier is connected to submissions, normally all variations grouped in one application are basing on the same dossier version. This may lead to inconsistencies, in case one or more of the included variations are revoked. At the very least, archiving must be carefully carried out and controlled. And as already mentioned, dossier maintenance is even more difficult if Grouping is performed across several MAs.

4.4 Summary

The possibility of Grouping has been largely adopted by the pharmaceutical industry. Due to the simplicity of the procedure, particularly the Grouping of Type IA/IA_{IN} is now part of the routine work, which leads to a significant reduction of application numbers. Type IB and Type II Groupings are also used more and more frequently. Although, multi-product groups are only used exceptionally, Grouping across MAs represents a good opportunity to report certain changes, e.g. a change in the DDPS.

The issues regarding the request for Grouping-permission are expected to decline with the growing CMDh list on acceptable and not acceptable Groupings.

Nevertheless, a further harmonisation between the different CAs regarding the procedure itself and the connected timelines is desirable.

Overall though, the introduction of Grouping is a full success.

5. Worksharing

With Commission Regulation (EC) 1234/2008 the possibility of the so-called Worksharing was introduced. Worksharing represents a single variation application procedure, which includes the same Type IB or Type II variation or a group of variations with at least one Type IB or Type II variation and which affects more than one MA of the same holder[32].

5.1 Advantages

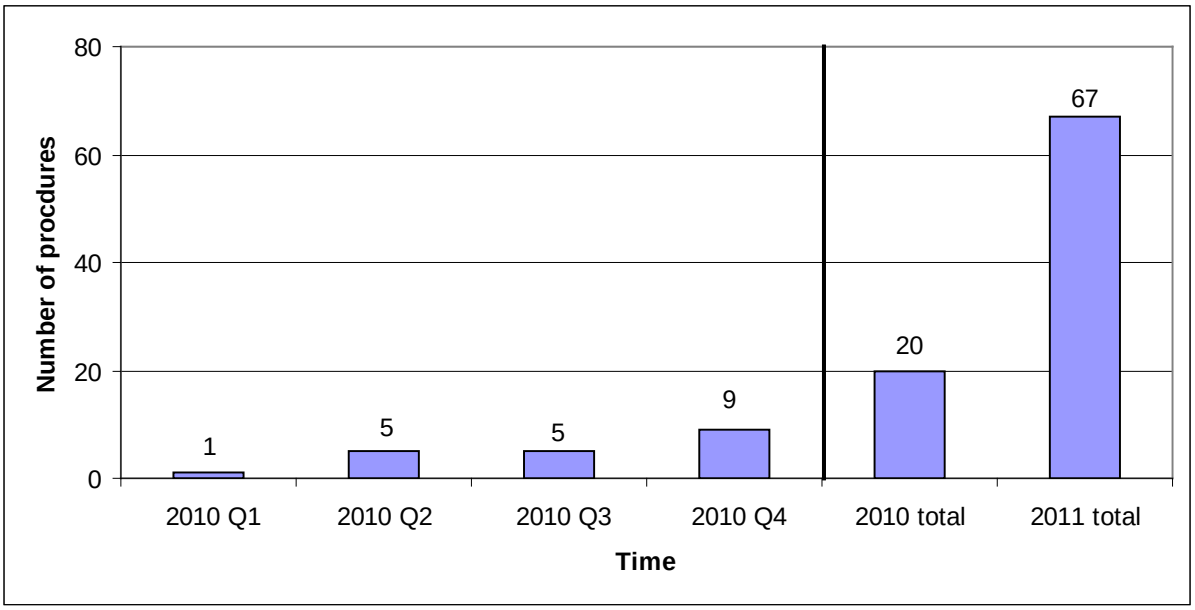
In contrast to the Grouping procedure, the major advantage of Worksharing from a MAHs perspective is not the decrease of workload, but the certainty to receive only one assessment outcome regarding all involved MAs, independently of the concerned CA or assessor. This is extremely favourable, as final assessments of variation applications often vary, especially depending on the assessing RMS but also on the assessor. Worksharing therefore leads to further harmonisation especially for MAs, basing on the same dossier, e.g. parallel DCPs with different RMS. Worksharing is useful as the maintenance of one harmonised dossier is drastically simplified with a common outcome of variation applications with the same content.

5.2 Usage and Progress of Worksharing

Due to the complex procedure, Worksharing was adopted quite hesitantly from the pharmaceutical industry. As Figure 7 shows, only 20 Worksharing procedures were started at CMDh in 2010. Especially at the beginning, only few requests were received.
In 2011, the amount was more than tripled with 67 Worksharings started.

[32] Commission Regulation (EC) 1234/2008, Article 20

Figure 7: Worksharing Procedures Started at CMDh



Source: CMDh - Statistics 2010 / 2011

At the EMA, 111 requests for Worksharing were already received in 2010. With 112 requests in 2011, this amount remained nearly constant.[33]

The in comparison higher amounts of Worksharing procedures at the EMA can be explained by the following fact: If at least one MA affected by the respective Worksharing is registered via a centralised procedure, the EMA is always the reference authority.

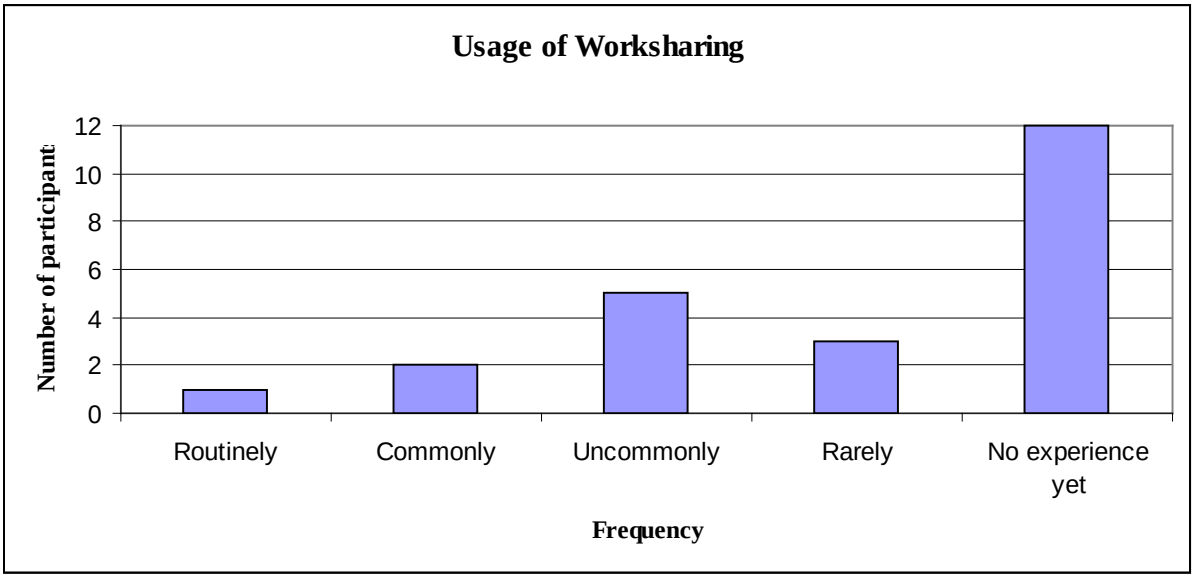
Nevertheless, the low Worksharing numbers registered by the CMDh and the EMA show that Worksharing, in contrast to Grouping, has not yet become part of the routine in the Regulatory Affairs Departments of pharmaceutical companies.

Survey outcome

This statement is also underlined by the respective survey outcome: The utilization of a Worksharing procedure is still an exceptional procedure – most of the 23 survey participants do not even have any experience with it yet (please refer to Figure 8).

[33] EMA - Monthly statistics report: April 2012

Figure 8: Survey outcome - Frequency of the Worksharing utilisation



Source: Survey on the Commission Regulation (EC) No 1234/2008, attached in Annex 2

The hesitant use of Worksharing is most likely caused by several different reasons.
First of all, Worksharing is only suitable for changes "with either no or limited need for assessment of a potential product-specific impact." Thus, all changes that require an individual assessment for each medicinal product concerned do not benefit from Worksharing.[34]

As a consequence, Worksharing is only useful for changes that are independent from the related products, such as DDPS updates or SmPC changes on the basis of PhVWP recommendations. Changes that depend on the different properties of the related products, such as changes to the manufacturing process or changes to the specifications are not suitable for Worksharing. Thus, the use of Worksharing is limited by its applicability.

Moreover, a Worksharing procedure is quite complex and linked with several challenges. This may also have an effect on the usage.

5.3 Challenges

Worksharing requires intensive planning

As already mentioned above, the Worksharing procedure is complex and thus requires a very intensive and proactive planning.

[34] CMDh Best Practice Guides for the Submission and Processing of Variations in the MRP, Rev. 16 (Chapter 7)

The MAH is advised to announce an upcoming Worksharing procedure to the CMDh at least 3 months prior to the planned submission. This pre-submission information must for example include a list of concerned MAs and a description of the variation itself.[35] In order to have all this information available 3 months in advance of the planned submission, the MAH must plan the preparation considerably earlier.

To reduce the complexity of Worksharing, a new approach was introduced for procedures with only one RMS. In case all involved products have the same RMS, the MAH does not have to submit the pre-submission information to the CMDh, but directly to the RMS. In turn, the respective RMS assesses whether or not the intended submission can be agreed to as a Worksharing procedure. The CMDh is only informed by the RMS or is involved if not agreed upon.[36]

This decrease in administrative burden was desired by the pharmaceutical industry and proposed in the comments to public consultation paper "Review of Commission Regulation (EC) No. 1234/2008", e.g. by the "Bundesverband der Pharmazeutischen Industrie" (BPI).[37] Thus, this adaption has been welcomed by the pharmaceutical industry, since Worksharing is simplified by it.

In addition, a welcomed side effect of the early cooperation between the MAH and the RMS might be a smooth handling of the procedure.

Nevertheless, a Worksharing procedure must be carefully planned and a good coordination of the internal process is crucial.

Worksharing is time-intensive

As mentioned above, the announcement of an upcoming Worksharing procedure must be submitted to the CMDh at least 3 months prior to the planned submission date. Afterwards, it takes approximately 1 month to receive the permission for Worksharing.

To avoid a further extension of timelines from the CMDh's side, the MAH must also take into account the CMDh meetings schedule. An announcement for Worksharing can only be discussed during a CMDh meeting, if the pre-submission information is received 2 weeks prior to it.[38]

[35] CMDh Best Practice Guides for the Submission and Processing of Variations in the MRP, Rev. 16 (Chapter 7)
[36] CMDh Best Practice Guides for the Submission and Processing of Variations in the MRP, Rev. 16 (Chapter 7)
[37] BPI comments to public consultation "Review of Commission Regulation (EC) No. 1234/2008", 18/10/2011
[38] CMDh Best Practice Guides for the Submission and Processing of Variations in the MRP, Rev. 16 (Chapter 7)

It should also be noted that the preparation of the final Worksharing submission is also highly time-consuming. Especially if many MAs are involved, it is a challenge to maintain all affected dossiers. This is particularly an issue for NeeS or eCTD submissions, as a new sequence is required for each dossier. Thus, enough time and man-power must be available in order to update all concerned dossiers.
In addition, a robust data management system is essential to keep the archive up-to-date.

The timetable for a Worksharing assessment after its actual submission is 60 days. Therefore, the timelines for included Type IB variations are also prolonged, as the timetable for a stand-alone Type IB variation is only 30 days.[39] This should be taken into consideration by the applicant.

Finally, another time-critical aspect must also be considered by the MAH. During a repeat-use procedure or a renewal, no variations should be submitted. Thus, it must be ensured that none of these procedures is ongoing or is to be submitted during an intended Worksharing procedure and this has to be ensured for all involved MAs. Other open changes must also be taken into account in order to retain consistent regulatory compliance.
As a consequence, a foresighted planning of a Worksharing procedure is important in order to fix a suitable time point for submission.

Taking into account the extended time for the preparation and the Worksharing procedure itself, Worksharing is only feasible for variations that allow a long phase of preparation. It is not suitable for changes that must be implemented relatively instantly.

5.4 Summary

Right after its legal introduction, Worksharing was used very hesitantly. Although the use is continuously increasing now, the experience with Worksharing is still limited. But it can be expected that due to the growing use, the companies will get more and more familiar with the procedure as well as the required planning and preparation. This again may enhance the courage in companies to submit more Worksharing applications and may therefore further increase the procedure's importance.

[39] Commission Regulation (EC) 1234/2008, Articles 9, 20

Furthermore, the simplification of the process should also encourage companies to use Worksharing more frequent.

The main advantage to receive only one outcome of assessment within Europe for all involved MAs is highly favourable and thus important for the pharmaceutical industry, especially as companies work more and more globally.

6. Type IB by default

In the former Commission Regulations (EC) 1084/2003 and 1085/2003, minor changes of Type IA or Type IB were defined by being listed in the associated Annex I and by fulfilling the conditions set out therein. Major Type II variations were defined as a variation that cannot be deemed to be a minor variation or an extension of a MA as given in Annex II[40]. Thus, all changes that were not listed in Annex I or II or which would not fulfil the given conditions, did automatically require a Type II variation (= Type II by default).

With Commission Regulation (EC) 1234/2008, Type IA and Type II variations are now classified in the Classification Guideline. A Type IB variation is currently defined as a variation, which is not an extension and which is not classified in the Classification Guideline (= Type IB by default).[41]

Therefore, classification of unlisted variations has in general been switched from Type II to Type IB.

With this switch, the responsibility for considering the impact of changes to a medicinal product on its quality, safety and efficacy lies now more with the applicant. This is reasonable as the MAH should know the affected medicinal product best and variations to the medicinal product are mostly applicant driven.[42]

Nevertheless, a safeguard clause in the Variation Regulation allows the CA to reclassify a variation from Type IB to Type II, in case the CA considers the change to have a significant impact on quality, safety or efficacy.[43] This ensures an appropriate assessment of all variations, but also involves the risk of prolonged timelines for the MAH.

6.1 Positive experience

From the very beginning, the paradigm change defining unlisted variations as a Type IB rather than a Type II variation was highly appreciated by the pharmaceutical industry.[44]

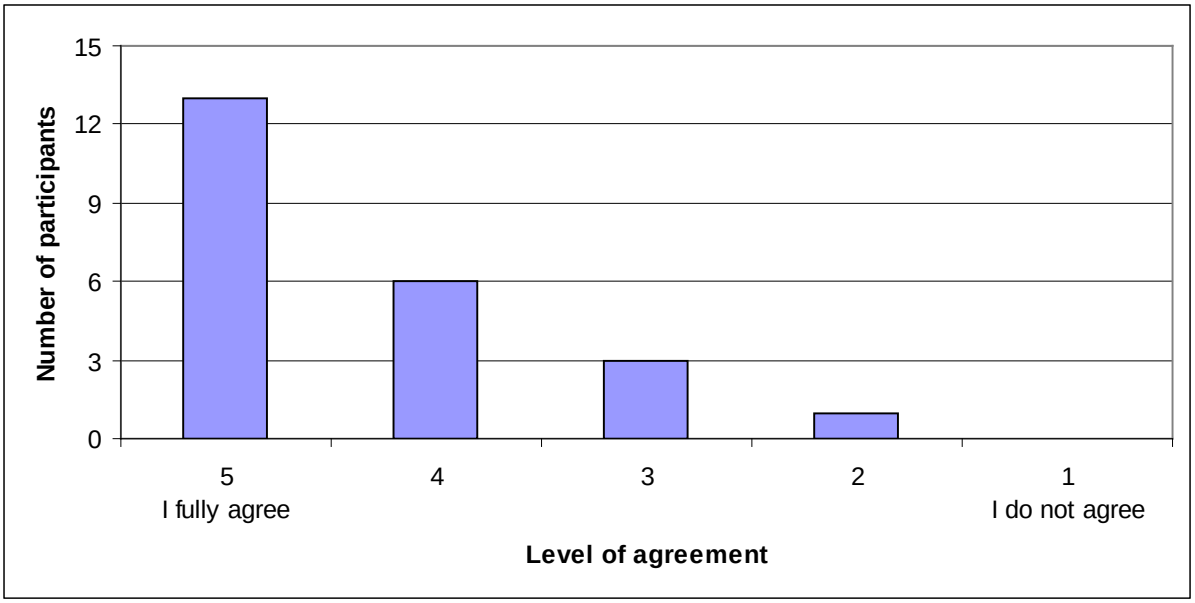
Survey outcome

Two and a half years after the applicability of the new Variation Regulation, this legal update is still regarded as an improvement.

[40] Commission Regulations (EC) No 1084/2003 and (EC) No 1085/2003
[41] Commission Regulation (EC) No 1234/2008
[42] Study documentation MDRA-13, Modul 5
[43] Commission Regulation (EC) No 1234/2008, Article 2
[44] Comments of BPI concerning Better Regulation of Pharmaceuticals; Version: 24 October 2007, page 6

As Figure 9 shows, 19 from 23 participants in the survey, fully or mostly agree with statement that Type IB by default is an improvement. None of the participants does not agree at all.

Figure 9: Survey outcome – Level of agreement on the statement: Type IB by default in general is an improvement



Source: Survey on the Commission Regulation (EC) No 1234/2008, attached in Annex 2

The positive experience with Type IB by default can be explained by the two major advantages linked with this innovation – the reduced costs and the reduced timelines.

Reduced costs

In most member states, (exception are the member states requiring an annual fee), the fees for a Type IB variation are significantly lower than the fees for a Type II variation.

Thus the switch from the variation classification Type II by default to Type IB by default has a significant impact on the budget of Regulatory Affairs Departments.

Reduced assessment timelines

The assessment time frame for a Type IB variation (30-days time frame) is shorter than for a Type II variation (60 or 90-day time frames). As a consequence, the timelines for implementation of such changes are cut down due to the new Variation Regulation and Type IB by default. This on the one hand side decreases the time-pressure in Regulatory Affairs Departments and on the other hand side increases the flexibility of the supply management.

6.2 Negative experience

The legally assured fact that Type IB variations can be deemed as accepted if the CA has not send the MAH its opinion within 30 days[45], should actually simplify the planning of implementation dates and make them more reliable.

Unfortunately this opportunity does not play an essential role in practice.

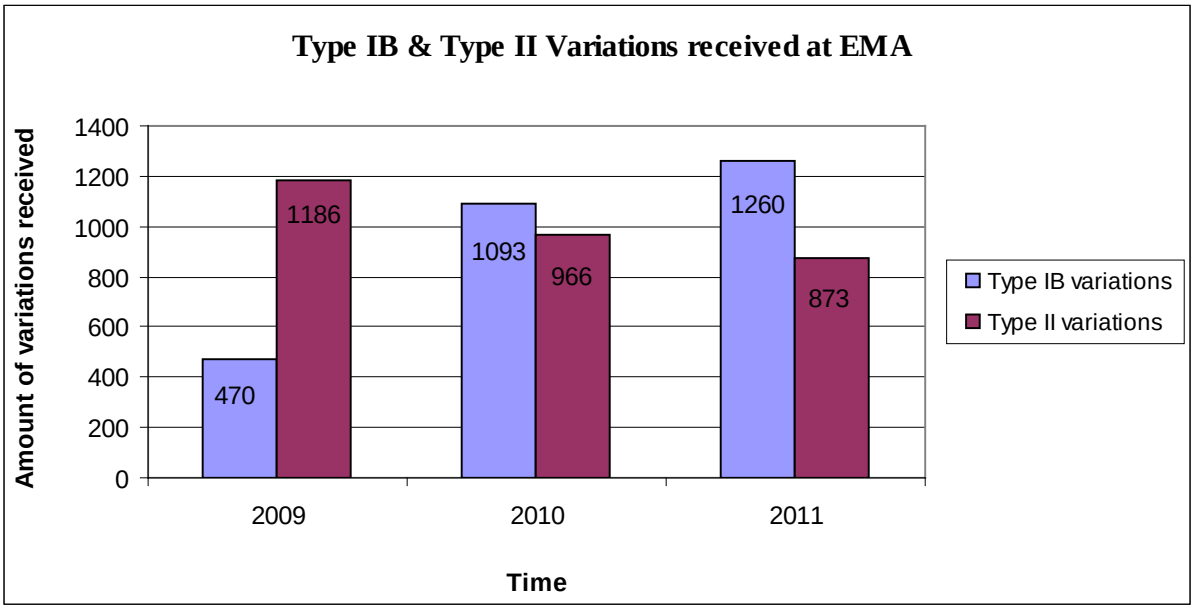
First of all, the 30-day period is counted only after validation. And since validation is often delayed, the opportunity to implement a change after 30 days is quite meaningless in practice.[46]

And second, implementation of a variation after 30 days, without a formal approval bears the risk on later comments and therefore an impact on the potentially already marketed product. Therefore, for some changes, such as a change in product information, it is feasible to wait for the formal approval. In any case, the MAH should be aware of the potential risk and decide on the implementation after 30 days on a case-by-case basis.

6.3 Impact on variation distribution

Due to the switch to Type IB by default, the distribution of the variation types changed. As expected, the number of Type II variations decreased while number of Type IB variations increased. This is illustrated by the number of variations received at the EMA, shown in Figure 10.

Figure 10: Type IB & Type II Variations received at EMA from 2009 to 2011



Source: EMA - Monthly statistics report: April 2012

[45] Commission Regulation (EC) No 1234/2008, Article 9
[46] EGA contribution to the EC public consultation on the variations regulation 1234/2008/EC

In 2009, prior to the applicability of the new Variation Regulation, clearly more Type II variations than Type IB variations were received. This changed in 2010, where more IB variations were received. The effect was even more obvious in 2011.

Another observable phenomenon triggered by the new Classifcation Guideline is the fact that the total number of Type II variations only decreased by approximately one third while the number of Type IB variations more than doubled. This effect is discussed in more detail in chapter 8.

6.4 Summary

The switch from Type II by default to Type IB by default is definitely regarded as improvement by the pharmaceutical industry. It reduces the cost for unforeseen variations and shortens the timelines for implementation. Especially the second aspect is important as the long timelines for Type II variations often led to a delay in implementation, in the past.

Regarding the delay in validation it is proposed to specify and reinforce the legislative timeline related to Type IB variations in order to "constitute a sufficient basis for a timely implementation of Type IB variations."[47]

[47] EGA contribution to the EC public consultation on the variations regulation 1234/2008/EC

7. Article 5 procedure

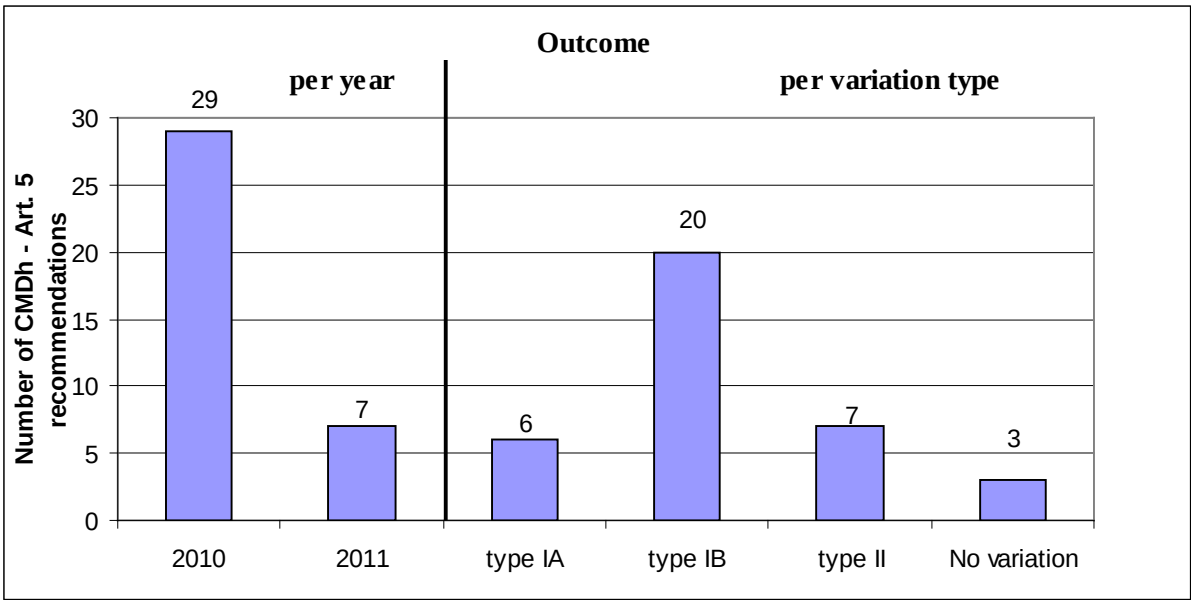
As explained before, the Type IB by default rule enables the applicant to submit any unlisted change as a Type IB variation, so-called unforeseen variations, without prior consultation of the CA.

Additionally, the MAH has the legal right to ask the CMD or the EMA for a scientific recommendation on the classification of unlisted changes with the Article 5 procedure.[48] The Type IB variations basing on an Article 5 recommendation, together with the Type IB variations exemplary listed in the Classification Guideline and finally the Type IB variations not meeting all conditions of a classified Type IA variation are defined as foreseen Type IB variations.

7.1 Usage and Progress

Overall 36 recommendations in connection with an Article 5 procedure were given by the CMDh in 2010 and 2011. The majority of the recommendations was already given in 2010 (please refer to Figure 11).

Figure 11: CMDh – Art. 5 recommendations on variation classification



Source: CMDh - Statistics for New Applications (MRP/DCP), Art. 29 CMDh Referrals and Art. 5 Variation 2010 / 2011

[48] CMDh Best Practice Guides for the Submission and Processing of Variations in the MRP, Rev. 16 (Chapter 8)

This may be caused by the fact that all scientific recommendations are published following deletion of commercial confidential information. Thus, all other MAHs can also refer to the already given recommendation and must not run an own Article 5 procedure. Additionally, the given recommendations can help the applicant by the assessment of related changes.
The survey also confirmed that the CMDh List "Recommendations for unforeseen variation according to Article 5"[49] is helpful for the applicants, as shown in Figure 12.

7.2 Advantages

An Article 5 procedure provides the instrument to clarify any uncertainties regarding the classification of unlisted changes. Thus, the timelines for assessment and consequentially for implementation are more reliable with a respective classification recommendation.
In consequence, a reclassification of a Type IB to a Type II variation with prolonged timelines can be avoided. In addition, an Article 5 procedure might be useful for a change considered to be a Type IA variation by the MAH. Without a respective recommendation by CMD or the EMA, this change would have to be submitted as a Type IB variation involving higher costs and longer timelines.

7.3 Challenges

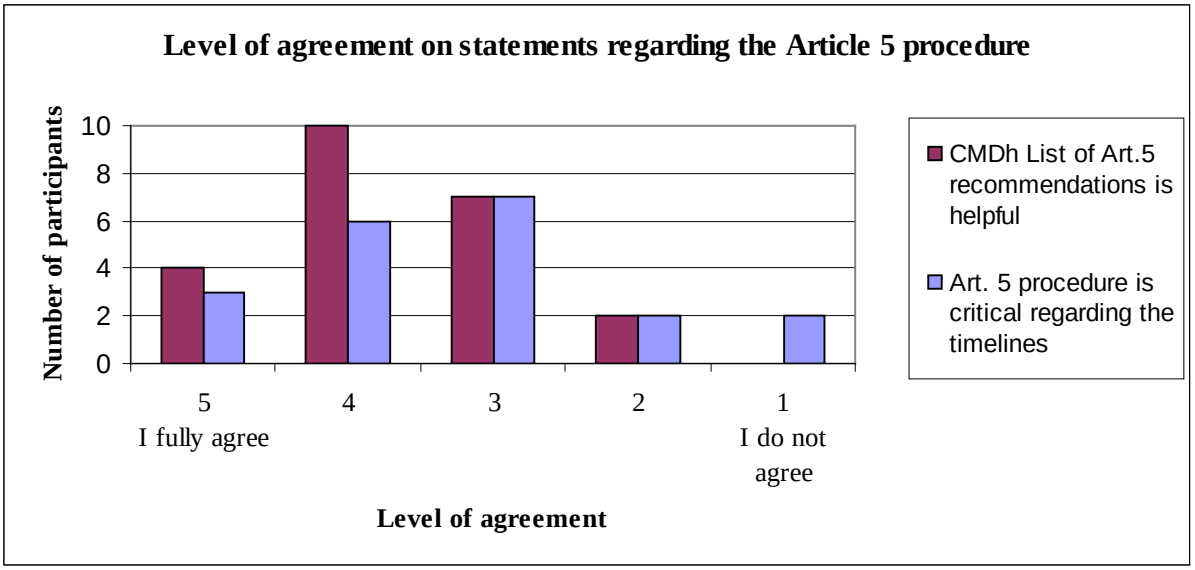
The scientific recommendation on variations according to Article 5 of the new Variation Regulation is given by the CMD/EMA within 45 days. Although this is an appropriate timeline for the required assessment, it leads to a delay in submission and implementation. In case recommendation is requested at CMDh, specific submission dates should also be considered, in order to give the CMDh the opportunity of discussing the request during one of their monthly meetings.[50] Overall, an Article 5 procedure can be critical regarding the timelines and must be planned accurately in advance of the actual variation submission. Thus, an Article 5 procedure may not be feasible for urgent variations.

[49] CMDh Recommendations for classification of unforeseen variation according to Article 5
[50] CMDh Best Practice Guides for the Submission and Processing of Variations in the MRP, Rev. 16 (Chapter 8)

Survey outcome:

As Figure 12 shows, 16 from 20 participants (3 abstentions) in the survey at least partly agree with the statement that an Article 5 procedure is critical regarding the timelines.

Figure 12: Survey outcome – Level of agreement on various statements regarding the Article 5 procedure



Source: Survey on the Commission Regulation (EC) No 1234/2008, attached in Annex 2

7.4 Summary

Although, the Article 5 procedure may not be suitable for time-critical variations, it offers clarity for the MAH regarding timelines and costs of unforeseen variations. This is especially useful for variations that bear the risk to be reclassified to a Type II variation or that are expected to be classified as a Type IA variation.

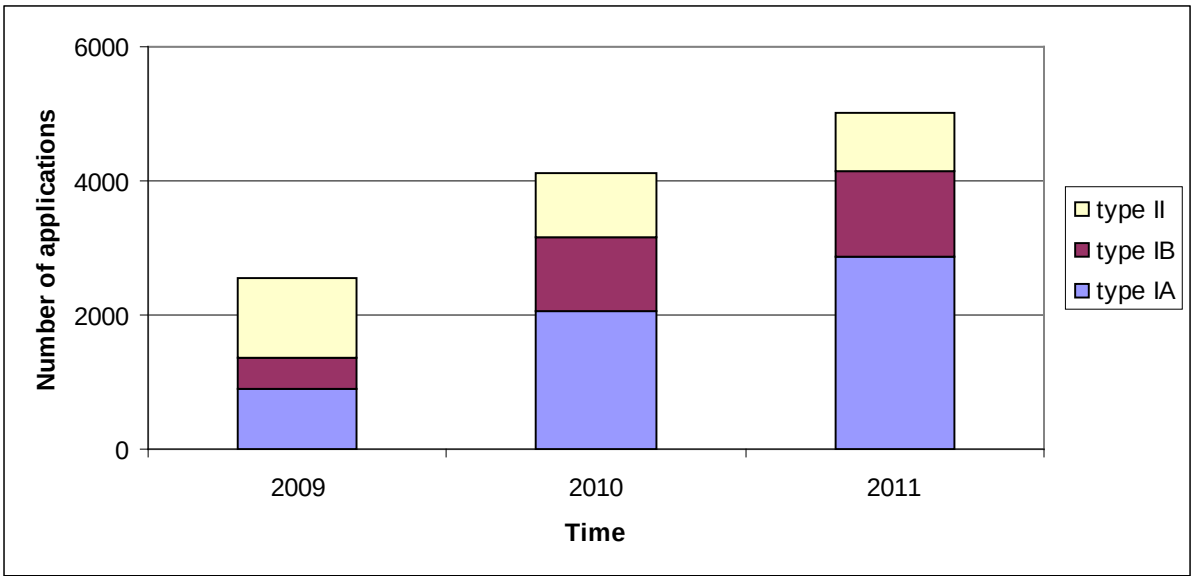
The fact that the recommendations are published and all MAHs can refer to the procedure outcome is a remarkable benefit for the pharmaceutical industry as a whole.

Nevertheless, the number of Article 5 procedures is still quite low. Thus, in order to reach the goal of a comprehensive Classification Guideline, the pharmaceutical industry should use this opportunity more often.

8. Total amount and distribution of variations

The innovations connected with the new Variation Regulation, in particular with the introduction of Type IB by default, have an impact on the total number and distribution of submitted variations in the EU. This is illustrated by Figure 13.

Figure 13: Number of variation applications received at EMA



Source: EMA - Monthly statistics report: April 2012

Two effects of the new Variation Regulation are to be observed from this illustration:
To begin with, significantly more variations were received by the EMA in 2010 and 2011 in comparison to 2009. And secondly, the distribution of the variation types changed. Both effects are discussed below.

8.1 Distribution of submitted variations

The distribution of submitted variations shifted with the new Variation Regulation: the number of Type II variations decreased while the number of Type IA and Type IB variations increased. As already mentioned in chapter 6, this is partially caused by the change of default variations from Type II to Type IB. According to the EMA this effect is also the result of "the newly introduced classification guideline that resulted in the downgrading of variations from Type II to Type IB and Type IA".[51]

[51] EMA annual report 2010/2011

8.2 Total number of submitted variations

Figure 13 shows that the total number of variations submitted to the EMA nearly doubled from 2009 to 2011. The increase of variations is, besides the increasing number of centralised MAs, most likely triggered by the fact that the new classification also results in a considerably higher amount of defined variation types.[52] In the Annexes of Commission Regulation (EC) 1084/2003 only 51 Type IA and 60 Type IB variations were listed. Thus, a total of 111 variations were defined. [53] In the new Classification Guideline, this number was significantly increased to 126 Type IA/IA_{IN}, 29 Type IB and 86 Type II variations, resulting in 241 defined variations.[54] Therefore, more than twice as many variations are now defined in comparison to the former situation.

8.3 Summary

As expected, the switch to variation Type IB by default and the downgrading of Type II variations with the new Variation Regulation triggered a shift in the distribution of submitted variations regarding the variation types: Type IA and Type IB variations increased, whereas Type II variations decreased. This is in general a benefit for the pharmaceutical industry as the costs and the timelines for most changes are consequentially also decreased. However, the increased variation aspects included in the new Classification Guideline triggered an increased total number of variations to be submitted, which again generates higher workload and costs.

[52] EMA annual report 2010/2011
[53] Commission Regulation (EC) No 1084/2003, Annex 1
[54] Classification Guideline

9. Omission of the Umbrella Type II variation

It was formerly accepted by most agencies that various related or consequential changes were submitted as one comprehensive Type II variation, here referred to as Umbrella Type II variation. For an extensive dossier update, it was common practice, to submit only one Type II variation for the product part and one Type II variation for the substance part, covering all required changes.

With the new Variation Regulation and the introduction of Type IB by default, this option was basically cancelled. Now every change must be submitted as separate variation, as a single or within a grouped application. This fact has doubtlessly contributed to the increase of variations, illustrated in the former chapter.

9.1 Effects

Next to its impact on the amount of variations, the cancellation of the Umbrella Type II has an impact on workload and costs for Regulatory Affairs in pharmaceutical industry.

Increased workload

Even though, with the introduction of Grouping several variations can be submitted in one application now, additional tasks must be carried out regarding Type IB and Type II variations, e.g. requesting a grouping permission or including a justification for grouping. This was formerly not required.

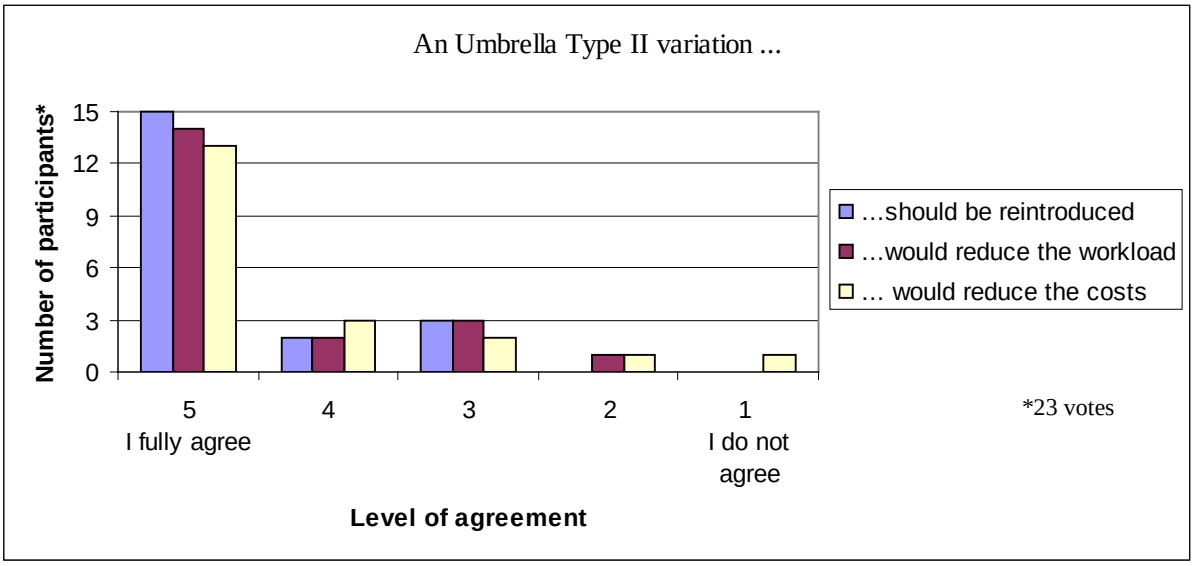
Increased costs

In most countries, a Type IB variation is much cheaper than a Type II variation. Nevertheless, as formerly several Type IB and Type IA variations could be included in the Umbrella Type II variation, the submission of one comprehensive Type II variation instead of many single variations often led to reduced variation fees. Therefore, an applicant had the opportunity to decide case-by-case if an Umbrella Type II was useful, taking into account the costs and the timelines for assessment.

Survey outcome

The survey confirmed that the opportunity to submit several changes as one single Type II variation is still desired by the pharmaceutical industry. As Figure 14 points out, nearly all participants in the survey fully or mostly agree with the statement that an Umbrella Type II variation should be re-introduced and also that this would reduce workload and costs.

Figure 14: Survey outcome - Level of agreement on various statements regarding the Umbrella Type II variation



Source: Survey on the Commission Regulation (EC) No 1234/2008, attached in Annex 2

9.2 Partial reintroduction

As the demand for an Umbrella Type II has also been noticed by the agencies, this possibility is now given again for determined aspects, e.g. for the update of module 1 in order to conform the current legislation incl. Braille, Readability user testing etc., or for an update of an ASMF in case of substantial changes.[55] Although limited to these aspects, the reintroduced opportunity is highly appreciated by the pharmaceutical industry.

9.3 Summary

The omission of the Umbrella Type II variation has contributed to the increase of variations and consequently induced higher workload and costs. Regarding the workload, this effect is mostly mitigated by the possibility of Grouping and Worksharing. Nonetheless, the re-introduction of an Umbrella Type II variation for at least further determined aspects should be taken into account.

[55] CMDh Q/A-List, Questions 3.4, 4.12

10. Changes to the documentation without changing the medicinal product

A variation is required for any change to the marketing authorisation dossier. This statement is true for addition, replacement or deletion of information, unless amendments to the dossier only concern editorial changes[56].

Despite the above stated definition given in the Classification Guideline, all variation aspects listed in the Guideline are associated with a change to the medicinal product and not with a change only affecting the documentation.

The Classification Guideline does not include variation aspects exclusively referring to a change/update in the documentation, such as inserting new stability data without changing the shelf life or replacing a process validation protocol by a process validation report.

This already represented a deficiency in the former Commission Regulations 1084/2003 and 1085/2003. However, at the time it was mostly accepted by the CAs to perform additional updates of the dossier not affecting the finished product's quality without any additional variation.

10.1 Current situation

Currently, any revision of the dossier that is not plainly editorial requires an individual variation Type IB unforeseen, since an update of the dossier solely performed to keep the documentation up-to-date but not connected to product-related changes is not listed in the Classification Guideline.

This may lead to unreasonable situations. For example, a change in the batch size of the finished product is normally submitted via a Type IA variation, whereas the inclusion of the finalised validation report would require a Type IB variation, and therefore lead to higher fees. Even more so, since the connected documentation update is not a legal requirement, the applicant would effectively be fined for submitting this kind of variation.

10.2 Potential of solely documentation-related variations

It is no legal requirement to supplement a dossier with additional information/data, if the respective medicinal product is not affected by it. Nonetheless, updating the related documentation might be advantageous, e.g. prior to a renewal procedure or in the preparation process of a repeat-use procedure.

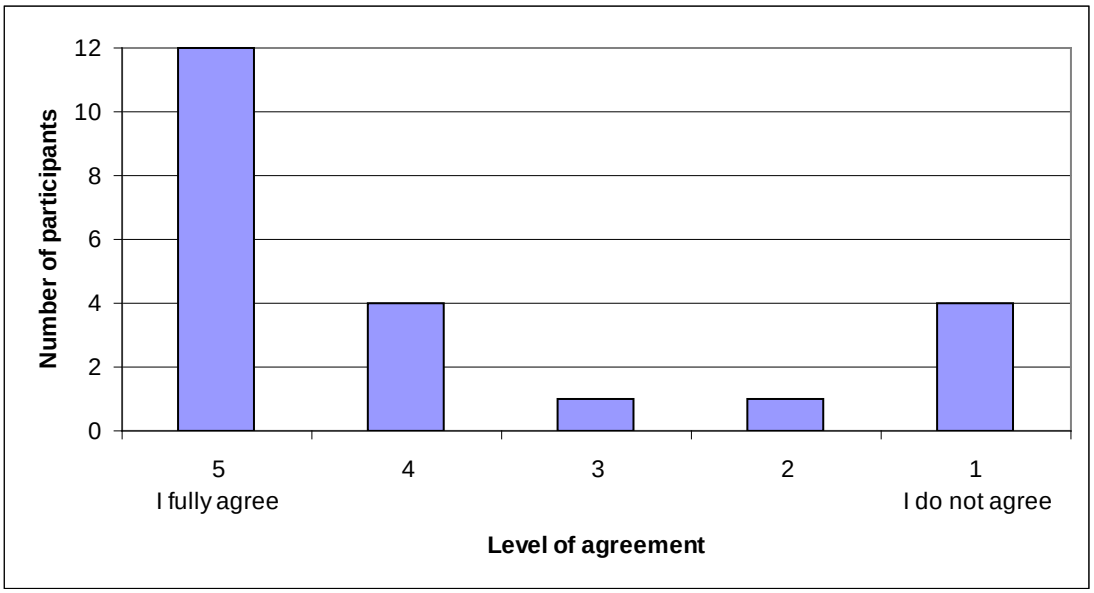
[56] Classification Guideline

In any case, an up-to-date and complete documentation regarding a specific medicinal product, which provides the current knowledge on its manufacture and quality specificities, e.g. documenting all performed ICH stability data, is desirable.
And as soon as all purely nationally authorised MAs will also fall in the scope of the new Variation Regulation, a simple opportunity to update a dossier in accordance with current data on the drug product will become even more important as the documentation of older national MAs tend not to be maintained as well as the ones authorised via MRP/DCP or even CP.

Survey outcome

As Figure 15 shows, most of the 23 participants of the performed survey agreed with the statement that changes of the dossier, which do not affect the medicinal product as such, are missing in the Classification Guideline.

Figure 15: Survey outcome – Level of agreement that variations concerning a dossier update without changing the medicinal product are missing in the Classification Guideline



Source: Survey on the Commission Regulation (EC) No 1234/2008, attached in Annex 2

10.3 Summary

The introduction of a simple and inexpensive possibility, e.g. via defined Type IA variations, to update the documentation of a pharmaceutical product without changes to its manufacture and quality specificities, would facilitate up-to-date and comprehensive dossiers. Therefore, it should be considered to include appropriate variations in the Classification Guideline.

11. Costs of variations

The impact of the new Variation Regulation on variation costs is difficult to determine as its effects potentially connected to variation costs are diverse and divergent. In addition, the scales of variation fees vary greatly among the CAs and thus among the member states.

11.1 Impact of the innovations of Commission Regulation (EC) 1234/2008

The innovations of the new Variation Regulation have divergent effects on the costs of variations:

On hand, the switch from variation Type II by default to Type IB by default should generally reduce variation costs for the MAHs since fees for Type IB variations are abundantly lower than for Type II variations.

On the other hand, the increased number of variation aspects and the concomitant increase of the total number of submitted variations might result in a rise of costs for regulatory variation submissions. Furthermore, the lost option to submit an Umbrella Type II variation potentially also leads to an increase in submitted variations and thus also in higher costs.

Therefore, it is hard to predict if the new Variation Guideline will result in a de- or increase of costs for variation. This might strongly depend on each MAH.

11.2 Fee structure of the MS

The costs of variations differ strongly between countries. Some countries, e.g. The Netherlands, do not charge fees per variation, but charge an annual fee for each MA. For these countries, the new Variation Regulation should not have any impact on the costs.

Other countries have already adapted their scale of fees to the new procedural options offered by the new Variation Regulation. For example, UK introduced a fee for Grouping and Austria introduced a fee for an Annual Report application.[57] This is favourable, as besides a reduction of regulatory costs for the MAH, this measure also encourages and rewards the utilisation of the newly introduced procedural options. In turn and since Annual Report, Grouping and Worksharing are all supposed to decrease the workload for the CAs in general, this measure is also in favour of the respective authority.

Countries, which have not yet adapted their respective scale of fees after the new Variation Regulation has come into effect, e.g. Germany, should therefore consider this step as well.

[57] MHRA, Fees for licence variations applications; Verordnung des BASG über den Gebührentarif

11.3 Estimated impact

In the scope of the public consultation regarding the revision of the Variation Regulation 1234/2008, the European Generic Medicines Association (EGA) observed a general increase of regulatory expenses for variations.[58]

The outcome of the herein discussed survey mostly supports this evaluation. However, it could not provide a distinct opinion of the participants: While, approximately one half of the participants stated that the total costs for variations increased in comparison to the former Variation Regulation, the other half indicated that the costs remained almost unchanged. Nonetheless, the fact that no participant stated that the costs for variations decreased suggests an overall increase of post-authorisational regulatory costs for most MAHs.

Thus, it can be concluded that the innovations increasing the variation costs (e.g. more variation aspects and concomitantly a higher total number of submitted variations) most likely outweigh the innovations reducing variation costs (e.g. Type IB by default instead of Type II by default).

11.4 Summary

From the survey it can be assumed that the new Variation Regulation mostly increased the total costs of variations in Regulatory Affairs Departments. The adaptation of fees to the new procedural options in several countries is favourable and should also be considered by countries that have not yet changed their fee scale for variations. Other possibilities to re-decrease the regulatory costs for variation applications again are suggested by the EGA in its comments to the public consultation on the revision of the Variation Regulation 1234/2008. The suggestions include the re-introduction of Umbrella Type II variations, as well as better distinction between individual product-related changes and the company's related changes.[59] Overall a re-evaluation of the currently charged variation fees should be carried out.

This will be especially important once the national MAs are subjected to the new Variation Regulation, which might trigger a further increase of regulatory costs.

[58] EGA contribution to the EC public consultation on the variations regulation 1234/2008/EC
[59] EGA contribution to the EC public consultation on the variations regulation 1234/2008/EC

12. Suggestions for further improving the new Variation Regulation

Several suggestions for a further improvement of the current Variation Regulation were included in the comments to the public consultation on the "Review of Commission Regulation (EC) No. 1234/2008", from October 2011 by the pharmaceutical industry. For example, BPI and EGA both stated their opinion on this particular subject.
The herein presented suggestions for further improvement of the Variation Regulation have been developed, taking into account these comments and the outcome of the previous chapters.

12.1 Suggestions

"Do and tell"

An official statement regarding the timeline for an "immediate notification" would be favourable. Furthermore and in favour of the pharmaceutical industry, the defined timeframe should not be chosen to be too small in order to still and realistically be able to submit these variations in time: The newly gained regulatory flexibility should not be restricted again by the chosen timeline.

Annual Report

The BPI suggests an alignment of the EU Annual Report with the US annual report system by allowing the submission of the EU Annual Report within 60 days of the 1-year reporting period.[60] As most pharmaceutical companies are operating globally, this option would lead to further harmonisation of procedures.

Grouping

As suggested in chapter 4 of the present master thesis, the procedure and timelines for a Grouping-permission should be further harmonised among the authorities in order to ensure a consistent handling within Europe.

Worksharing

BPI suggested decreasing the administrative burden related to Worksharing by simplifying the process in case only one RMS is included.[61] This is already implemented and included in the CMDh Best Practice Guide. This was a big step forward from an industrial point of view.

[60] BPI comments to public consultation "Review of Commission Regulation (EC) No. 1234/2008", 18/10/2011
[61] BPI comments to public consultation "Review of Commission Regulation (EC) No. 1234/2008", 18/10/2011

Another aspect that should be considered is the alignment of the two different timetables regarding a Type IB variation as part of a Worksharing procedure (60 days) versus the submission as individual variation (30 days). The currently specified, prolonged timeline of a Type IB Worksharing procedure may prevent its regular use due to its extended duration.

Variation Type IB

The EGA considers the option to implicitly implement a Type IB variation after 30 days, which is legally allowed by the new Variation Regulation, as basically meaningless. A timely implementation is critical, as the 30-day period is counted only after validation and validation is often delayed.

It is therefore suggested, defining the timelines for a Type IB variation, especially focussing on the time for validation, more precisely and harmonised within the EU in order to create a basis for implementation of these Variations after 30 days not only in theory but also in practice.[62]

Umbrella Type II Variation

As stated in chapter 9, the re-introduction of an Umbrella Type II variation would be advantageous for MAHs. Such types of variations – even if they were only possible for certain further change aspects – should enable the reduction of regulatory expenses and workload. The EGA shares this point of view, as this option would be of particular importance for generic companies holding a large amount of MAs.

Inclusion of additional variation aspects

Variation aspects related to an update or a supplementation of the authorised dossier without actual changes to the medicinal product, are suggested to be included in the Classification Guideline. This would offer a simple opportunity to keep the applicant's dossier up-to-date, as already discussed in chapter 10 of the present master thesis.

Costs

In general, it would be favourable if EU member states that have not yet adapted their fee system to the newly introduced proceedings of the new Variation Regulation would consider to do so in the near future. The EGA, for example, suggest further consideration on the calculation of variation fees for Grouping. For example, it is proposed that fees for a single

[62] EGA contribution to the EC public consultation on the variations regulation 1234/2008/EC

Grouping should not exceed the fees for a Type II variation.[63] This suggestion is particularly significant, in case the re-introduction of Umbrella Type II variations is not taken into account.

Downgrading of variation types

A further downgrading of variations is recommended by the BPI.

For example, the re-classification of a CEP update to Type IA rather its submission as variation Type IA_{IN} would increase flexibility.

Furthermore, a general classification for variations introducing new side-effects, contraindications, etc. as Type IA variations would most likely improve the safety of a medicinal product and simplify the procedure to keep SmPC and the patient information leaflet up-to date.[64]

12.2 Summary

The above mentioned suggestions are all driven by three major objectives of the pharmaceutical industry: the decrease of costs, the reduction of timelines and the simplification of procedures.

These objectives are clearly motivated by the fact that expenses and timelines always have been and still are critical parameters in connection with regulatory submissions.

Nonetheless, several suggestions of the pharmaceutical industry, intended to improve the new Variation Regulation have already been implemented. Examples are the simplified Worksharing procedure for MAs with the same RMS or the permission of Grouping of variations across several MAs with different RMS countries.

It remains to be seen to what extent suggestions of the pharmaceutical industry regarding the new Variation Guideline, e.g. communicated by the BPI or the EGA and given in the comments to the public consultation on the review of the new Variation Regulation, will be considered.

[63] EGA contribution to the EC public consultation on the variations regulation 1234/2008/EC

[64] BPI comments to public consultation “Review of Commission Regulation (EC) No. 1234/2008”, 18/10/2011

13. Overall conclusion

The major objectives of the Commission Regulation (EC) 1234/2008 were to design the regulatory environment "simpler, clearer and more flexible and to reduce the administrative burden".[65]

Two and a half years after the Regulation's implementation it can be stated, that these objectives have been achieved - but only to a certain extent.

The new tools introduced with the update of the Variation Regulation have generally been accepted by the pharmaceutical industry.

This is particularly the case for "Do and tell" applications, Grouping and IB by default, as these tools are very user-friendly in practice.

The flexibility in Regulatory Affairs Departments has been increased by the introduction of "Do and tell", and Grouping has a positive effect on the workload connected to regulatory submissions. The major advantages of Type IB by default are reduced timelines as well as expenses for variations.

And although there are still challenges linked with these new regulatory tools, their advantages clearly outweigh these challenges.

Other tools such as the Annual Report and Worksharing are only used hesitantly until now.

In theory, the Annual report is supposed to increase the flexibility in connection with regulatory submissions. And Worksharing was introduced to facilitate a further harmonisation by guarantying a common outcome of the respective variation assessment throughout Europe. However, these tools are quite complex and linked with major challenges, which again restrict their practicability.

On the whole, the introduction of the new Variation Regulation is generally regarded as an improvement by the pharmaceutical industry, but there is still room for further improvement.

[65] Commission Regulation (EC) No 1234/2008

14. Outlook

With the implementation of Directive 2009/53/EC and the amending Directives 2001/82/EC and 2001/83/EC in national law and the update of Commission Regulation (EC) 1234/2008, the Variation Regulation will also have to be applied to purely national MAs.[66] This harmonisation is a significant challenge, since the majority of MAs (more than 80%) in the EU are purely national authorisations at the moment.[67]

Currently the new Variation Regulation is not yet compulsive with regard to national MAs and thus the related legal situation varies across Europe: Some MS have already implemented the new Variation Regulation voluntarily on January 01, 2010, other MS followed later. On the other hand, several MS have not yet implemented the Regulation at a national level. Therefore, the regulatory environment in Europe is very heterogeneous at the moment. It is consequentially an enormous challenge for Europe-wide operating companies to currently manage the submission, requirements and implementation of variations to MAs.[68]

The consistent implementation of the new Variation Guideline for nationally authorised medicinal products is therefore favourable for pharmaceutical companies operating in more than one European MS.
Nevertheless, this also represents a significant challenge, depending on the present situation in the respective MS. The topic was included in the public consultation "Review of Commission Regulation (EC) No. 1234/2008" in order to receive comments by all affected parties, including the authorities and the pharmaceutical industry.

In Germany, where the new Variation Regulation is not implemented for nationally authorised MAs yet, this step will affect the variation system to a considerable extent.

As the national variation system in Germany according to § 29 of the "Arzneimittelgesetz" (AMG)[69] is plain, easy to understand and perform as well as efficient, most companies benefit from it. [70]

[66] Directive 2009/53/EC
[67] Public consultation paper - Review of the Variation Regulations
[68] Public consultation paper "Review of Commission Regulation (EC) No. 1234/2008" - Final EFPIA/EVM/EBE comments
[69] Gesetz über den Verkehr mit Arzneimitteln
[70] BPI comments to public consultation "Review of Commission Regulation (EC) No. 1234/2008", 18/10/2011

The advantages of this particular national variation system, such as

- the potential combination of several change aspects by means of a single national application, basically representing the option of an extensive grouping of variations
- a system-conform, feasible submission of variations without fixed conditions and mandatory documentation
- virtually no administrative burden
- the little number of variation types requiring official approval
- lower costs of national variations versus the respective MRP/DCP fees

are evident. Therefore, this system is still highly convenient for the resident pharmaceutical industry.

Thus in case of Germany, the implementation of the new Variation Regulation is expected to immensely increase workload and costs as well as prolong the timelines of regulatory submissions. In general, it will be a major challenge to manage all MAs with the European variation system. It will require additional man power and increased budgets for the Regulatory Affairs Departments.
In order to at least attenuate the prolonged timelines of the new Variation Regulation, the BPI requests shorter timelines for purely nationally authorised MAs.[71]
To avoid a significant increase of variation costs it is also suggested to not simply adopt the current fees raised for European variations, but to revise the entire scale of fees.

Overall, the effect of the inclusion of purely national MAs into the scope of the new Variation Regulation will further promote harmonisation. Nonetheless, it will also be challenging industry and in turn the affected authorities.
The individual effect will strongly depend on the respective country. It remains to be seen, how the individual MS will cope with this challenge.

[71] BPI comments to public consultation “Review of Commission Regulation (EC) No. 1234/2008”, 18/10/2011

15. Summary

On 01st of January 2009, Commission Regulation (EC) No 1234/2008 entered into force, replacing the former Commission Regulations 1084/2003 and 1085/2003. The new Variation Regulation should design the regulatory framework "simpler, clearer and more flexible, without compromising public and animal health and reduce administrative burden".[72]
In order to achieve this objection, several innovations were introduced, such as "Do and tell", Annual Report, Worksharing, Grouping and Type IB by default.
Since 01st of January 2010, the new Variation Regulation is applicable for all MAs registered via CP, MRP or the Decentralised Procedure (DCP).

The retrospective assessment of the new Variation Regulation two and half years after its applicability showed that the newly introduced tools have a great impact on the work in Regulatory Affairs Departments.
With the help of a survey on Commission Regulation (EC) No. 1234/2008, including 23 participants from 18 different companies, the general assessment of the Variation Regulation and the impact of its innovations on the practical work was estimated.

The offered options of the revised Variation Regulation were adopted by the pharmaceutical industry to a varying extent, depending on their usability in practice.
Next to the advantages provided by the new tools, such as an increased flexibility, decreased workload and downgraded variation types, new challenges are linked to the usage of the diverse tools, such as the need for intensive tracking and strategic planning or the increased complexity of the dossier maintenance.
The last two years showed that Commission Regulation (EC) 1234/2008 influences the number of variations, the distribution per variation type and the total variation costs.

In sum, the options offered by the new variation regulation present the Regulatory Affairs Departments with several advantages and a new set of challenges.
It is concluded that the introduction of Commission Regulation (EC) 1234/2008 is regarded as an improvement by the pharmaceutical industry, but that there are still areas for improvement.

A short outlook indicates that, especially for Germany, the implementation of the Variation Regulation at a national level will change the variation system to a great extent and entail major challenges.

[72] Commission Regulation (EC) 1234/2008

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Survey on the Commission Regulation (EC) No 1234/2008
Attached in Annex 2

Verordnung des Bundesamtes für Sicherheit im Gesundheitswesen (BASG) **über den Gebührentarif** gemäß GESG, Gültig ab dem 28.11.2011
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Annexes

Annex 1
BfArM letter of 30 March 2012, Gesch.Z.: 13.2N-3413-108808/12

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Ihre Zeichen und Nachricht vom	Gesch.Z.: Bitte bei Antwort angeben	(0228) 99307-	Bonn,
12.03.2012	13.2N-3413-108808/12	4331	30. MRZ. 2012

Masterarbeit Variation Regulation

Sehr geehrte Frau Kamp,

zu Ihrer Anfrage können wir Ihnen nachfolgend aufgeführte Daten zur Verfügung stellen. Diese wurden aus AMIS ermittelt und umfassen nur Verfahren, die beim BfArM bereits erfasst sind. Aufgrund eines Bearbeitungsstaus insbesondere bei den Variations Typ IA/IB mit DE als CMS ist die Anzahl der Verfahren aus dem Jahr 2011, möglicherweise auch aus 2010, nicht abschließend. Wir verweisen auch auf die Möglichkeit, über DIMDI zu recherchieren.

1. Anzahl der beim BfArM eingereichten Variations Typ IA/IB/II

	RMS							
	IA single	IA grouped	IAIN single	IAIN grouped	IB single	IB grouped	II single	II grouped
2009	2963				1683		1500	
2010	856	214	1050	503	2163	215	603	60
2011	582	314	785	717	2453	973	488	141

	CMS							
	IA single	IA grouped	IAIN single	IAIN grouped	IB single	IB grouped	II single	II grouped
2009	6022				2849		2971	
2010	1478	674	1555	1387	3826	827	1513	213
2011	867	561	960	832	2665	786	1379	335

2. Anzahl der beim BfArM eingereichten Worksharing-Verfahren

2010 32 (mit 190 beteiligten Zulassungen)
2011 64 (mit 748 beteiligten Zulassungen)
2012 11 (mit 65 beteiligten Zulassungen)

3. Anzahl der beim BfArM eingereichten Variations im Zusammenhang mit Design Space

Variations im Zusammenhang mit Design Space wurden nach unserer Recherche keine eingereicht.

Freundliche Grüße
Im Auftrag

Annett Möbius

Annex 2
Survey on the Commission Regulation (EC) No. 1234/2008

1. Overview

Purpose of the survey

The survey on the Commission Regulation (EC) No. 1234/2008 was carried out in June 2012, in order to assess the own practical experiences and opinions

The survey gathered feedback on the utilisation and the practicability of the Commission Regulation (EC) 1234/2008, focussing on the innovations connected with the Commission Regulation (EC) No. 1234/2008, other special topics and the effect on costs for variations.

Feedback

Feedback was received from 23 participants from 18 different companies.

From four companies feedback was received twice, as the survey was completed by two employees each.

The companies that took part in the survey include several generic companies, originators, regulatory consultants and also one company producing veterinary medicinal products.

Thus, the survey covers a broad spectrum in the pharmaceutical sector.

Information requested

The level of agreement to several statements to Commission Regulation (EC) No. 1234/2008 was requested. The options for answering ranged from “5” meaning “I fully agree” to “1” meaning “I do not agree”.

In some cases, also the extent of usage was requested with the following optional choices: 5: routinely, 4: commonly, 3: uncommonly 2: rarely, 1: no experience yet.

Information included in this Annex:

a) The used questionnaire (blank)
b) Tabulation of the survey outcome
c) Tabulated individual results (anonymized)

The original returned surveys can be provided on request.

a) Questionnaire (blank)

Survey on the Commission Regulation (EC) No 1234/2008

Name:

Company:

Department:

With this questionnaire, a retrospective assessment of the Commission Regulation (EC) 1234/2008 should be carried, out two and half years after its applicability.

Several statements concerning different innovations of the new variation regulation are stated.

Please tick the appropriate box on the right side, depending on the extent of your agreement with the given statement, whereas 5 means "I fully agree" and 1 means "I do not agree".

	5	4	3	2	1
1. IA - "Do and tell"					
1) "Do and tell" in general is an improvement	☐	☐	☐	☐	☐
2) Workload is decreased by "Do and tell"	☐	☐	☐	☐	☐
3) "Do and tell" increases the flexibility in the RA department	☐	☐	☐	☐	☐
4) Time pressure is decreased by "Do and tell"	☐	☐	☐	☐	☐
5) Following challenges are linked with the "Do and tell" procedure:					
- Fixing the implementation dates	☐	☐	☐	☐	☐
- Tracking of implementation/submission dates	☐	☐	☐	☐	☐
- Timelines for "immediate notification"	☐	☐	☐	☐	☐
- National MAs are not yet scope of the new regulation	☐	☐	☐	☐	☐
- "Tell and do" is not an option anymore	☐	☐	☐	☐	☐
2. IA – Annual report					
1) Annual report in general is an improvement	☐	☐	☐	☐	☐
2) Annual report is used *(5: routinely, 4: commonly , 3: uncommonly 2: rarely, 1: no experience yet)*	☐	☐	☐	☐	☐
3) Workload is decreased by an annual report	☐	☐	☐	☐	☐
4) IA variations are combined with IA_{IN} or other upcoming variation instead of waiting for the annual report *(5: routinely, 4: commonly , 3: uncommonly 2: rarely, 1: no experience yet)*	☐	☐	☐	☐	☐
5) Following challenges are linked with an annual report:					
- Tracking of implementation/submission dates	☐	☐	☐	☐	☐
- Rejection may have an impact on marketed products	☐	☐	☐	☐	☐
- GMP documents are not in line with the dossier for along time	☐	☐	☐	☐	☐

	5	4	3	2	1
3. Grouping:					
1) Grouping in general is an improvement	☐	☐	☐	☐	☐
2) Workload is decreased by Grouping	☐	☐	☐	☐	☐
3) Grouping is used for *(5: routinely, 4: commonly , 3: uncommonly 2: rarely, 1: no experience yet)*					
- Type IA variations	☐	☐	☐	☐	☐
- Type IB variations	☐	☐	☐	☐	☐
- Type II variations	☐	☐	☐	☐	☐
- Supergroupings (grouping across different MAs)	☐	☐	☐	☐	☐
4) CMDh list of possible groupings is helpful	☐	☐	☐	☐	☐
5) Following challenges are linked with Grouping:					
- Request for Grouping permission is time intensive	☐	☐	☐	☐	☐
- Rejections due to unaccepted groupings	☐	☐	☐	☐	☐
4. Worksharing					
1) Worksharing in general is an improvement	☐	☐	☐	☐	☐
2) Workload is decreased by Worksharing	☐	☐	☐	☐	☐
3) Worksharing is used *(5: routinely, 4: commonly , 3: uncommonly 2: rarely, 1: no experience yet)*	☐	☐	☐	☐	☐
4) Worksharing is useful if at least ____ MAs are included *(Please insert a number)*					
5) Following challenges are linked with Worksharing:					
- Request for Worksharing at CMDh is time intensive	☐	☐	☐	☐	☐
- Worksharing requires intensive planning	☐	☐	☐	☐	☐
- Preparation of a Worksharing procedure is time intensive	☐	☐	☐	☐	☐

	5	4	3	2	1
5) IB by default					
1) IB by default in general is an improvement	☐	☐	☐	☐	☐
2) Number of variations is increased by IB by default	☐	☐	☐	☐	☐
3) Article 5 procedure is used *(5: routinely, 4: commonly , 3: uncommonly 2: rarely, 1: no experience yet)*	☐	☐	☐	☐	☐
4) Article 5 procedure is critical regarding the submission timelines	☐	☐	☐	☐	☐
5) The CMDh List "Recommendations for unforeseen variation according to Article 5" is helpful	☐	☐	☐	☐	☐
6) Others					
1) An "umbrella type II" variation (covering several changes)					
- should be reintroduced	☐	☐	☐	☐	☐
- would reduce the workload	☐	☐	☐	☐	☐
- would reduce the costs	☐	☐	☐	☐	☐
2) Variations concerning a dossier update without changing the product (e.g. inserting a validation report or stability data) are missing in the variation guideline	☐	☐	☐	☐	☐
3) Number of total variations (compared to the former variation regulation) *(please tick the appropriate)* - Decreased - Remained almost unchanged - Increased					☐ ☐ ☐
4) Total costs for variations (compared to the former variation regulation) *(please tick the appropriate)* - Decreased - Remained almost unchanged - Increased					☐ ☐ ☐
5) Other experiences or comments:					

b) Tabulation of the survey outcome

Ranges:

Level of agreement: 5: I fully agree
1: I do not agree

Extent of usage: 5: routinely
4: commonly
3: uncommonly
2: rarely
1: no experience yet

1. IA - "Do and tell"

Statement: "Do and tell" in general is an improvement

Level of agreement	Number of participants	Mean value
5	16	4.64
4	4	
3	2	
2	0	
1	0	
Abstention	1	

Statement: Workload is decreased by "Do and tell"

Level of agreement	Number of participants	Mean value
5	3	2.68
4	3	
3	6	
2	4	
1	6	
Abstention	1	

Statement: "Do and tell" increases the flexibility in the RA department

Level of agreement	Number of participants	Mean value
5	9	3.91
4	6	
3	4	
2	2	
1	1	
Abstention	1	

Statement: Time pressure is decreased by “Do and tell”

Level of agreement	Number of participants	Mean value
5	8	3.73
4	5	
3	5	
2	3	
1	1	
Abstention	1	

Statement: Following challenges are linked with the “Do and tell” procedure:
1. Fixing the implementation dates

Level of agreement	Number of participants	Mean value
5	13	4.32
4	4	
3	4	
2	1	
1	0	
Abstention	1	

2. Tracking of implementation/submission dates

Level of agreement	Number of participants	Mean value
5	9	4.00
4	6	
3	5	
2	2	
1	0	
Abstention	1	

3. Timelines for “immediate notification”

Level of agreement	Number of participants	Mean value
5	9	3.73
4	4	
3	5	
2	2	
1	2	
Abstention	1	

4. National MAs are not yet scope of the new regulation

Level of agreement	Number of participants	Mean value
5	8	3.68
4	4	
3	7	
2	1	
1	2	
Abstention	1	

5. “Tell and do” is not an option anymore

Level of agreement	Number of participants	Mean value
5	4	2.48
4	0	
3	6	
2	3	
1	8	
Abstention	2	

2. IA – Annual Report

Statement: Annual Report in general is an improvement

Level of agreement	Number of participants	Mean value
5	9	4.04
4	6	
3	6	
2	1	
1	0	
Abstention	1	

Annual Report is used

Extent of usage	Number of participants	Mean value
5	2	2.41
4	4	
3	3	
2	5	
1	8	
Abstention	1	

Statement: Workload is decreased by an Annual Report

Level of agreement	Number of participants	Mean value
5	0	2.55
4	4	
3	7	
2	8	
1	3	
Abstention	1	

IA variations are combined with IAIN or other upcoming variation instead of waiting for the annual report

Extent of usage	Number of participants	Mean value
5	8	3.82
4	9	
3	1	
2	1	
1	3	
Abstention	1	

Statement: Following challenges are linked with an Annual Report:
1. Tracking of implementation/submission dates

Level of agreement	Number of participants	Mean value
5	11	4.05
4	4	
3	5	
2	1	
1	1	
Abstention	1	

2. Rejection may have an impact on marketed products

Level of agreement	Number of participants	Mean value
5	11	4.14
4	6	
3	3	
2	1	
1	1	
Abstention	1	

3. GMP documents are not in line with the dossier for a long time

Level of agreement	Number of participants	Mean value
5	9	3.82
4	4	
3	6	
2	2	
1	1	
Abstention	1	

3. Grouping

Statement: Grouping in general is an improvement

Level of agreement	Number of participants	Mean value
5	15	4.48
4	5	
3	2	
2	1	
1	0	
Abstention	0	

Statement: Workload is decreased by Grouping

Level of agreement	Number of participants	Mean value
5	4	3.22
4	7	
3	4	
2	6	
1	2	
Abstention	0	

Grouping is used for
1. Type IA variations

Extent of usage	Number of participants	Mean value
5	11	4.30
4	9	
3	2	
2	1	
1	0	
Abstention	0	

2. Type IB variations

Extent of usage	Number of participants	Mean value
5	7	3.74
4	8	
3	4	
2	3	
1	1	
Abstention	0	

3. Type II variations

Extent of usage	Number of participants	Mean value
5	3	2.43
4	2	
3	6	
2	3	
1	9	
Abstention	0	

4. Supergroups

Extent of usage	Number of participants	Mean value
5	2	1.87
4	1	
3	3	
2	3	
1	14	
Abstention	0	

Statement: CMDh list of possible groupings is helpful

Level of agreement	Number of participants	Mean value
5	4	3.61
4	9	
3	8	
2	1	
1	1	
Abstention	0	

Statement: Following challenges are linked with Grouping:
1. Request for Grouping permission is time intensive

Level of agreement	Number of participants	Mean value
5	3	3.09
4	6	
3	7	
2	4	
1	3	
Abstention	0	

2. Rejections due to unaccepted groupings after implementation

Level of agreement	Number of participants	Mean value
5	1	2.96
4	8	
3	7	
2	3	
1	4	
Abstention	0	

4. Worksharing

Statement: Worksharing in general is an improvement

Level of agreement	Number of participants	Mean value
5	8	3.83
4	6	
3	6	
2	3	
1	0	
Abstention	0	

Statement: Workload is decreased by Worksharing

Level of agreement	Number of participants	Mean value
5	0	2.55
4	2	
3	12	
2	4	
1	4	
Abstention	1	

Worksharing is used

Extent of usage	Number of participants	Mean value
5	1	2.00
4	2	
3	5	
2	3	
1	12	
Abstention	0	

Worksharing is useful if at least _X_ MAs are included
(Please insert a number)

Mean value	4.00
Range	2 - 10

Statement: Following challenges are linked with Worksharing:
1. Request for Worksharing at CMDh is time intensive

Level of agreement	Number of participants	Mean value
5	8	4.00
4	5	
3	6	
2	1	
1	0	
Abstention	3	

2. Worksharing requires intensive planning

Level of agreement	Number of participants	Mean value
5	9	4.25
4	7	
3	4	
2	0	
1	0	
Abstention	3	

3. Preparation of a Worksharing procedure is time intensive

Level of agreement	Number of participants	Mean value
5	9	4.25
4	7	
3	4	
2	0	
1	0	
Abstention	3	

5. Type IB by default / Article 5 procedure

Statement: Type IB by default in general is an improvement

Level of agreement	Number of participants	Mean value
5	13	4.35
4	6	
3	3	
2	1	
1	0	
Abstention	0	

Statement: Number of variations is increased by IB by default

Level of agreement	Number of participants	Mean value
5	1	2.48
4	3	
3	8	
2	5	
1	6	
Abstention	0	

Article 5 procedure is used

Extent of usage	Number of participants	Mean value
5	2	2.00
4	2	
3	3	
2	3	
1	13	
Abstention	0	

Statement: Article 5 procedure is critical regarding the submission timelines

Level of agreement	Number of participants	Mean value
5	3	3.30
4	6	
3	7	
2	2	
1	2	
Abstention	3	

Statement: The CMDh List “Recommendations for unforeseen variation according to Article 5” is helpful

Level of agreement	Number of participants	Mean value
5	4	3.83
4	10	
3	7	
2	2	
1	0	
Abstention	0	

6. Others

Statement: An “umbrella type II” variation should be reintroduced

Level of agreement	Number of participants	Mean value
5	15	4.6
4	2	
3	3	
2	0	
1	0	
Abstention	3	

Statement: An “umbrella type II” variation would reduce the workload

Level of agreement	Number of participants	Mean value
5	14	4.45
4	2	
3	3	
2	1	
1	0	
Abstention	3	

Statement: An “umbrella type II” variation would reduce the costs

Level of agreement	Number of participants	Mean value
5	13	4.3
4	3	
3	2	
2	1	
1	1	
Abstention	3	

Statement: Variations concerning a dossier update without changing the product are missing in the variation guideline

Level of agreement	Number of participants	Mean value
5	12	3.86
4	4	
3	1	
2	1	
1	4	
Abstention	1	

Number of total variations (compared to the former variation regulation)
(Please tick the appropriate)

Decreased	1
Remained almost unchanged	10
Increased	12

Total costs for variations (compared to the former variation regulation)
(Please tick the appropriate)

Decreased	0
Remained almost unchanged	11
Increased	12

c) Tabulated individual results (anonymized)

P = Participant
a = Abstention

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	P21	P22	P23
1. IA - "Do and tell"																							
1) "Do and tell" in general is an improvement	5	5	4	5	5	5	5	a	5	5	3	5	4	5	5	5	3	4	5	5	4	5	5
2) Workload is decreased by "Do and tell"	4	5	4	1	1	5	4	a	2	1	3	3	3	5	2	3	3	2	1	1	3	2	1
3) "Do and tell" increases the flexibility in the RA department	3	5	4	2	5	5	4	a	3	1	4	5	4	5	4	5	3	4	5	5	2	5	3
4) Time pressure is decreased by "Do and tell"	3	3	4	2	5	5	5	a	4	1	2	5	3	2	4	4	3	3	5	5	4	5	5
5) Following challenges are linked with the "Do and tell" procedure:																							
Fixing the implementation dates	3	5	5	5	5	3	5	a	4	5	5	3	3	2	4	4	5	4	5	5	5	5	5
Tracking of implementation/submission dates	4	4	5	3	5	3	5	a	3	5	5	3	4	2	4	4	5	2	4	5	5	5	3
Timelines for "immediate notification"	3	3	2	5	3	5	5	a	1	5	4	3	3	2	4	1	5	4	5	5	4	5	5
National MAs are not yet scope of the new regulation	5	3	3	2	5	5	4	a	4	5	5	3	3	4	3	1	3	4	5	5	5	3	1
"Tell and do" is not an option anymore	3	1	1	2	5	1	2	a	1	3	3	5	3	5	1	1	2	1		3	3	5	1
2. IA – Annual report																							
1) Annual report in general is an improvement	4	5	4	5	5	3	5	a	5	5	3	4	4	2	3	5	3	4	4	5	3	5	3
2) Annual report is used	4	3	2	2	2	1	5	a	1	3	5	1	4	2	1	2	1	1	1	4	3	1	4
3) Workload is decreased by an annual report	2	3	2	3	3	3	3	a	1	3	1	2	2	1	3	4	2	2	4	4	4	2	2
4) IA variations are combined with IA_{IN} or other upcoming variation instead of waiting for the annual report	5	3	2	4	5	4	5	a	4	4	4	5	4	5	1	4	1	1	5	5	5	4	4
5) Following challenges are linked with an annual report:																							
Tracking of implementation/submission dates	4	5	5	3	5	3	5	a	4	5	5	2	4	1	3	3	5	4	5	5	5	5	3
Rejection may have an impact on marketed products	4	5	4	5	5	5	5	a	5	4	5	5	3	1	3	4	4	4	5	5	3	5	2
GMP documents are not in line with the dossier for a long time	5	5	3	5	5	3	5	a	2	5	4	5	4	2	3	3	4	3	4	5	3	5	1

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	P21	P22	P23
3. Grouping:																							
1) Grouping in general is an improvement	3	5	4	5	5	5	5	2	5	5	5	3	5	5	5	4	4	4	5	4	5	5	5
2) Workload is decreased by Grouping	3	3	2	4	5	2	4	2	3	4	1	1	2	5	2	4	4	2	5	4	4	5	3
3) Grouping is used for																							
Type IA variations	3	3	2	4	5	5	4	5	4	5	4	5	4	5	5	5	4	4	4	4	5	5	5
Type IB variations	2	3	2	4	5	1	4	3	4	3	4	5	4	5	3	5	4	4	4	2	5	5	5
Type II variations	1	3	2	2	1	1	3	3	3	2	4	5	1	5	1	1	4	1	1	1	3	3	5
Supergroupings (grouping across different MAs)	1	3	1	1	1	1	3	3	2	5	1	4	1	2	1	1	1	1	1	1	2	1	5
4) CMDh list of possible groupings is helpful	3	5	3	3	3	4	2	3	4	5	3	4	5	4	1	3	4	4	4	4	4	5	3
5) Following challenges are linked with Grouping:																							
Request for Grouping permission is time intensive	5	4	3	3	5	2	5	1	3	1	4	2	4	3	1	2	4	2	3	4	4	3	3
Rejections due to unaccepted groupings after implementation	3	4	3	4	4	3	5	1	2	2	1	4	4	2	4	3	4	4	3	1	3	3	1
4. Worksharing																							
1) Worksharing in general is an improvement	5	5	4	5	5	4	2	3	5	5	3	2	4	4	4	2	3	3	4	3	3	5	5
2) Workload is decreased by Worksharing	3	3	3	4	1	1	2	2	2	3	3	1	2	a	3	1	3	3	4	3	3	3	3
3) Worksharing is used	4	3	1	1	1	2	5	2	1	2	3	1	3	1	1	3	4	1	1	1	1	1	3
4) Worksharing is useful if at least _X_ MAs are included *(Please insert a number)*	3	a	2	a	7	5	5	2	a	3	2	a	5	a	a	2	3	a	a	10	5	a	2
5) Following challenges are linked with Worksharing:																							
Request for Worksharing at CMDh is time intensive	3	5	3	5	5	2	5	3	4	5	4	5	4	a	3	3	4	a	a	4	5	5	3
Worksharing requires intensive planning	4	3	4	4	5	5	5	3	4	5	5	5	4	a	3	3	5	a	a	4	5	5	4
Preparation of a Worksharing procedure is time intensive	4	3	4	4	5	5	5	3	3	5	5	5	4	a	3	4	5	a	a	4	5	5	4
5) IB by default																							
1) IB by default in general is an improvement	3	5	4	5	5	3	5	5	5	5	4	5	4	4	2	4	3	4	5	5	5	5	5
2) Number of variations is increased by IB by default	2	3	4	2	3	2	3	1	1	1	4	1	4	2	3	3	3	2	1	3	3	1	5
3) Article 5 procedure is used	5	1	2	1	1	1	3	1	3	1	4	1	4	2	1	3	2	1	1	1	1	1	5
4) Article 5 procedure is critical regarding the submission timelines	5	3	3	4	5	3	3	1	2	3	4	4	3	2	3	a	1	a	a	4	5	4	4
5) The CMDh List "Recommendations for unforeseen variation according to Article 5" is helpful	3	4	3	4	4	4	3	4	3	5	2	4	5	4	3	4	3	4	5	4	3	5	2

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	P21	P22	P23
6) Others																							
1) An "umbrella type II" variation (covering several changes)																							
should be reintroduced	3	5	5	5	5	5	5	5	5	3	4	5	3	a	5	4	5	a	a	5	5	5	5
would reduce the workload	2	5	5	5	5	5	5	3	5	3	4	5	3	a	5	4	5	a	a	5	5	5	5
would reduce the costs	1	5	5	3	5	5	5	2	5	3	4	5	4	a	5	4	5	a	a	5	5	5	5
2) Variations concerning a dossier update without changing the product are missing in the variation guideline	3	5	4	5	5	5	1	4	4	1	5	5	5	2	1	5	a	4	5	5	5	5	1
3) Number of total variations (compared to the former variation regulation)																							
Decreased		x																					
Remained almost unchanged					x	x	x	x	x	x			x	x		x						x	
Increased	x		x	x							x	x			x		x	x	x	x	x		x
4) Total costs for variations (compared to the former variation regulation)																							
Decreased																							
Remained almost unchanged		x				x	x	x	x	x			x	x		x		x				x	
Increased	x		x	x	x						x	x			x		x		x	x	x		x

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

Angelika Kamp