Inclusion of the German purely national marketing authorisations in the scope of the Variations Regulation and use of the new Classification Guideline of 2013 in practice compared to the previous guideline and the former national German variation system

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List of Abbreviations

AMG	Arzneimittelgesetz (medicinal products act, the drug law of the Federal Republic of Germany)
AMGKostV	AMG Fees Ordinance (AMG-Kostenverordnung)
AMIS	Arzneimittelinformationssystem (BfArM Drug information system)
ASMF	Active Substance Master File
BAnz	Bundesanzeiger (Federal Law Gazette)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BMG	Bundesministerium für Gesundheit und Soziale Sicherung
BOB	Bundesoberbehörde
BPI	Bundesverband der Pharmazeutischen Industrie (German Pharmaceutical Industry Association)
CEP	Certificate of Suitability to the relevant Ph. Eur. Monograph
CESP	Common European Submission Platform
CMD	Coordination group for Mutual recognition and Decentralized procedure
CMDh	Coordination group for Mutual recognition and Decentralized procedure (human)
CMS	Concerned Member State
CP	Centralised Procedure
CTD	Common Technical Document
DCP	Decentralised Procedure
DDPS	Detailed Description of the Pharmacovigilance System
DGRA	Deutsche Gesellschaft für Regulatory Affairs
EC	European Commission
ENR	Einreichungsnummer (a specific submission number, derived from the national German MA-number)
EU	European Union
FAQ	frequently asked questions
IAIN	Type IA variations requiring immediate notification
MA	Marketing Authorisation

MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDRA	Master of Drug Regulatory Affairs
MHRA	Medicines and Healthcare products Regulatory Agency
MRP	Mutual Recognition Procedure
NTA	Notice to Applicants
OL	Official Journal of the European Union
PDF	Portable Document Format
Ph. Eur.	European Pharmacopoeia
PL	Package Leaflet
PSMF	Pharmacovigilance System Master File
QPPV	Qualified Person for Pharmacovigilance
QRD-Template	Templates provided by the Working Group on Quality Review of Documents (QRD) of the European Medicines Agency
RMS	Reference Member State
SCM	Supply Chain Management
SKNR	Structural Number (Strukturnummer; used to code a change item (Änderungstatbestand) in the AMIS data base
SmPC	Summary of product characteristics

Common terms and translated terms

German national variation	variation submitted for a German purely national MA according to the Variations Regulation in Germany
National variation	variation submitted for a purely national MA according to the Variations Regulation
Notification of change	‘Änderungsanzeige’, submission for a German purely national MA according to Section 29(1) AMG)

Change item	‘Änderungstatbestand’
Collective submission	‘Sammelanzeige’
Legal category	‘Verkaufsabgrenzung’
List of change items	‘Katalog der Änderungstatbestände’
Local representative	‘örtlicher Vertreter’

1 Introduction

During the life cycle of a product, usually many changes are made. This holds true for medicinal products after approval of the marketing authorisation application (MAA) as well, especially as the marketing authorisation holder (MAH) is obliged keep the dossier in accordance with the current state of scientific and technical progress.[1]
As the medicinal product and its approved dossier have to correspond, any change that affects the dossier of a licensed medicinal product triggers the submission of a variation to the relevant agencies. Hence, variations allow keeping the dossier and the marketing authorisation (MA) up to date during the life cycle of a licensed medicinal product on both sides, the MAH and the relevant agencies.

With the evolution of national drug laws in the last century, several different national systems evolved, each of them having their own system for registration and for notification of changes to the dossier. For more information, an excellent summary of the evolution of the German Medicinal Products Act (AMG; in German: Arzneimittelgesetz) and especially its Section 29, that deals with the requirements to notify changes to the MA, is given in the introduction of the master thesis of Dr. Verena Tautorat from 2011.[2]

With the introduction of the Centralised Procedure (CP) and the Mutual Recognition Procedure (MRP) in the European Union (EU) in 1995, an EU-wide, harmonised system for variations to the MAs granted by MRP became necessary to ensure that all the MAs related to one MRP remained harmonised.
Consequently, in parallel to the national systems, an EU-wide system for variations evolved. An excellent summary of the evolution of the EU-wide system for variations is presented in the introduction of the master thesis of Angelika Kamp from 2012.[3]

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[1] Directive 2001/83/EC, Article 23, OJ No L 311/79 of 28.11.2001, and Directive 2001/82/EC, Article 27, OJ No L 311/11 of 28.11.2001respectively.
[2] Dr. Verena Tautorat, MDRA master thesis, “The end of an era: Implementing Variation Directive 2009/53/EC into German Drug Law”, Bonn, 2011, http://dgra.de/media/pdf/studium/masterthesis/master_tautorat_v.pdf (15.02.2014; archived by WebCite® at http://www.webcitation.org/6NP0iItiR).
[3] Angelika Kamp, MDRA master thesis, “2 years Variation Regulation: A retrospective critical assessment from the industrial perspective”, Bonn, 2012, http://dgra.de/media/pdf/studium/masterthesis/master_kamp_a.pdf (15.02.2014; archived by WebCite® at http://www.webcitation.org/6NP1PZ4T8).

The end of this evolution was marked by Commission Regulation (EC) No 1234/2008 of 24.11.2008, also known as 'The Variations Regulation'. It is applicable since 01.01.2010 for all variations to MAs based on MRP/DCP and CP.

With Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009 amending Directive 2001/82/EC and Directive 2001/83/EC, as regards variations to the terms of marketing authorisations for medicinal products, it was intended to extend the scope of the Variations Regulation to purely national MAs[4] of all member states.

As the directive had to be transposed into national law, national peculiarities could be excepted. Consequent to Directive 2009/53/EC, Section 29 AMG was amended in October 2012[5] and below exceptions of the scope of the Variations Regulation were defined in Section 29(5) AMG:

- homeopathic medicinal products for human use that are subject to authorisation and were authorised before 01.01.1998 or were deemed to be authorised
- blood preparations listed in Article 3(6) of Directive 2001/83/EC (i.e. whole blood, plasma or blood cells of human origin which are exempted from the scope of Directive 2001/83/EG)
- tissue preparations authorised pursuant to Section 21, unless they are manufactured by a method involving an industrial process.[6]

In summary, the exemptions from the Variations Regulation are:

- standard marketing authorisations (Standardzulassungen) according to Section 36 AMG

[4] according to Commission Regulation (EC) No 1234/2008, Article 2, as amended by Commission Regulation (EU) No 712/2012 on 04.08.2013, "'Purely national marketing authorisation' means any marketing authorisation granted by a Member State in accordance with the acquis outside the mutual recognition or decentralised procedure and that has not been subject to a complete harmonisation following a referral procedure."

[5] Zweites Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften of 19.10.2012, Bundesgesetzblatt 2012 Part I no. 50, Bonn, 25.10.2012, p. 2192. http://www.bundesgerichtshof.de/SharedDocs/Downloads/DE/Bibliothek/Gesetzesmaterialien/17_wp/arzneimittelr2/bgbl.pdf;jsessionid=FEA7E44F2A5E4262F18A953D62905099.2_cid354?__blob=publicationFile (15.02.2014).

[6] AMG translation provided by the Language Service of the Federal Ministry of Health, http://www.gesetze-im-internet.de/englisch_amg/englisch_amg.html#p0723 (01.02.2014; archived by WebCite® at http://www.webcitation.org/6N3v8q3qK).

- homeopathic medicinal products for human use that are subject to authorisation (Section 29(5) AMG) and have been authorised or have been considered as authorised before 01.01.1998
- homeopathic registrations according to Section 38 AMG
- registrations of traditional herbal medicinal product, according to Sections 39a-d AMG
- parallel imports[7]

Directive 2009/53/EC amending the Directive 2001/82/EC and Directive 2001/83/EC, was a first step to include the purely national MAs in the scope of the Variations Regulation. In addition, the Variations Regulation (Commission Regulation (EC) No 1234/2008) had to be amended too. The necessary amendment was made by Commission Regulation (EC) No 712/2012 of 03.08.2012. This regulation amended the Variations Regulation in two steps as laid down in Article 2 and Article 3 of Commission Regulation (EC) No 712/2012.

First, the amendments dealing with clarifications, definitions and general updates of the Variations Regulation became effective on 02.11.2012.
These amendments included for example:

- Revised Article 5 procedure (Recommendation on unforeseen variations; holder cannot refer directly to CMD anymore but has to refer to relevant authority).
- Clarification that procedure and time lines for variations of type IB do not apply in case of grouping of IB with type II variations (Article 9).
- Possibility of extended time lines for groupings not listed in Annex III but agreed by the competent authority according Article 7(2)(c).
- Updated cross-references between the various articles of the Variations Regulation.

Second, on 04.08.2013, all amendments necessary for inclusion of the purely national MAs in the scope of the Variations Regulation became effective, especially Chapter IIa (Article 13a-f). The new Chapter IIa describes the notification procedure for national variations. The procedure corresponds to the MRP/DCP procedure but no CMS have to be mentioned. Nevertheless, the timelines to be applied on national variations are the same as for MRP/DCP procedures, even though no response time for CMS has to be provided for.

[7] Complete list translated from Dr. Michael Horn, “Historische Entwicklung des Arzneimittelrechts in Bezug auf Änderungsanzeigen und Umsetzung der Commission Regulation (EU) No 712/2012 - Variations in nationalen und europäischen Verfahren“, DGRA-Mitgliederworkshop, Bonn, 24.09.2013, p. 51.

As a consequence, besides the national exceptions, since 04.08.2013 all variations to MAs in the EU are regulated by the Variations Regulation. Considering the BfArM (Federal Institute for Drugs and Medical Devices), except the standard marketing authorisations, still 12.146 MAs and registrations are not and will not be under the scope of the Variations Regulation (3.860 homeopathic medicinal products for human use, 1.190 registered homeopathic and traditional herbal medicinal products and 7.096 MAs for parallel imports. On the other hand, 18.879 purely national MAs fall under the scope of the Variations Regulation since 04.08.2013 in addition to 11.811 MAs from MRP/DCP that had been under the scope of the Variations Regulation already (above figures as of 06.05.2013, Dr. Michael Horn, 2013[8]).
As a result, since 04.08.2013 the amount of MAs that the BfArM has to handle by the Variations Regulation has almost doubled.

When on 26.10.2012 the "Zweites Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften" of 19.10.2012 (also known as '16. AMG-Novelle') became effective, it did not only define the exceptions of the scope of the Variations Regulation as mentioned above, but it made another severe change in AMG Section 29(2a). This section lists the change items that are subject to approval. The change items requiring prior approval were amended by simply translating and adding the definition of a major variation of type II from Annex II (2)(d) of the Variations Regulation to Section 29(2a) number 4 AMG:

> "(d) variations related to substantial changes to the manufacturing process, formulation, specifications or impurity profile of the active substance or finished medicinal product which may have a significant impact on the quality, safety or efficacy of the medicinal product;"

Furthermore, exceptions related to changes to the withdrawal period for a veterinary medicinal product in Section 29(2a) number 6 AMG were deleted in order to achieve an adjustment to Annex II (2)(k) of the Variations Regulation:

> "(k) variations related to changes to the withdrawal period for a veterinary medicinal product."

In this manner Section 29(2a) AMG was harmonised with Annex II (2) of the Variations Regulation and now included all considerable changes that can have a clear effect on the quality, safety or efficacy of the medicinal product such as changes in the manufacturing process, the pharmaceutical form, specification or impurity profile of the active substance or the medicinal product.

[8] Dr. Michael Horn, "Historische Entwicklung des Arzneimittelrechts in Bezug auf Änderungsanzeigen und Umsetzung der Commission Regulation (EU) No 712/2012", DGRA-Mitgliederworkshop, Bonn, 24.09.2013.

In addition to this, the "Zweites Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften" of 19.10.2012 ('16. AMG-Novelle') introduced the new Section 29(2b) to the AMG. This section contains a list of five change items, that may be notified within twelve months following their implementation (first introduction of "do and tell" variations in the national German variation system). The five change items correspond to the type IA variations as defined in Annex II (1)(b-f) of the Variations Regulation. These are typical IA variations, such as changes to comply with a monograph of the pharmacopoeia, deletion of a manufacturing site or tightening of limits.

Consequent to the amendment of Section 29 AMG, new structural numbers (SKNR, in German: Strukturnummer) were introduced. SKNR's are used to code a change item (in German: Änderungstatbestand) in the AMIS data base. With almost all of them requiring prior approval and being almost directly translated from the former Classification Guideline[9], the national German variation system was from now on harmonised with the Variations Regulation and Classification Guideline in terms of which change items require prior approval.

The national German variation system applicable from 26.10.2012 until 04.08.2013 will be referred to as 'current national German variation system' henceforth as it is still valid for the exceptions of the scope of the Variations Regulation.

It should be mentioned, that the Variations Regulation and Classification Guideline are connected as explained in the introduction of the Classification Guideline:

> "Article 4(1) of the Variations Regulation charges the Commission with the task of drawing up guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of that Regulation as well as on the documentation to be submitted pursuant to these procedures."

Therefore an amendment of classification without changing the Variations Regulation is possible by updating the Classification Guideline.

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[9] former Classification Guideline: "Communication from the Commission - 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", effective from 22.01.2010 to 04.08.2013, OJ 2010/C 17/01, available at: http://ec.europa.eu/health/files/betterreg/pharmacos/classification_guideline_adopted.pdf (27.12.2013; archived by WebCite® at http://www.webcitation.org/6MBee7GYJ).

The Variations Regulation defines the principles of the classification in its Annex II. This Annex II defines that certain variations shall be classified as minor variations of type IA (such as administrative changes like contact details of a supplier).
In addition clear guidance is given in Annex II on variations that require a type II variation (such as a new indication or modification of existing therapeutic indication, as well as any variations related to changes outside the range of approved specifications, limits or acceptance criteria). The Classification Guideline is based on the principles laid down in Annex II of the Variations Regulation.

Before on 04.08.2013 all amendments necessary for inclusion of the purely national MAs in the scope of the Variations Regulation became effective, the Classification Guideline was updated on 16.05.2013. This new, updated Classification Guideline became effective on 04.08.2013 too and will be hereinafter referred to as updated Classification Guideline.[10]

This thesis investigates the above mentioned changes effective since 04.08.2013 and their consequences from an industrial point of view. In order to reduce the complexity and to keep this work concise and clearly laid out, this work focuses on human medicinal products that the BfArM is responsible for as competent authority.[11]
Moreover, MRP/DCP and German purely national MAs will be in the focus but not CP.
Likewise, extensions according to Annex I of the Variations Regulation are not within the scope of this work, as extension applications are handled like initial marketing authorisation applications (see updated Classification Guideline, sections 2.4.2. and 2.4.3.).
Lastly, urgent safety restrictions are excluded too, as they concern interim changes and follow a completely different process than variations (see updated Classification Guideline, section 2.6.).

[10] Updated Classification Guideline is the common term for document C (2013) 2804 (Brussels, 16.05.2013): Guidelines of 16.05.2013 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures. (12.02.2014, archived by WebCite® at http://www.webcitation.org/6NL3Bdi9l).

[11] Please note that the Paul Ehrlich Institute already accepts variation applications in accordance with the new variation regulation for purely national MAs since 01.01.2010 for veterinary medicinal products as described on page 32 of Dr. Verena Tautorat, DGRA master thesis, “The end of an era: Implementing Variation Directive 2009/53/EC into German Drug Law”, Bonn, 2011, http://dgra.de/media/pdf/studium/masterthesis/master_tautorat_v.pdf (15.02.2014; archived by WebCite® at http://www.webcitation.org/6NP0iItiR).

2 Issues under examination

In a first step, the differences between the former and updated Classification Guideline were analysed. This included the consideration of procedural changes as well as changes in categorisation or classification of variations. Secondly, differences between the former national German variation system and the European variation system as defined by the Variations Regulation and Classification Guideline were investigated.
Subsequently, potential consequences in practice of the differences found were drawn up.
Lastly, in order to assess the potential consequences a survey was conducted and evaluated.

2.1 Differences between former and updated Classification Guideline

2.1.1 Request of further information for IA variations

In contrast to the former Classification Guideline of 2010, the new, updated Classification Guideline was amended with procedural guidance on the handling of variations.
According to the paragraphs dealing with "Type IA variations review" (section 2.1.2., 2.1.3. and 2.1.4. for MRP, purely national procedure and CP respectively) a request of further information for type IA variations is possible for IA variations:

> "While in the case of minor variations of Type IA, failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the holder provides any missing documentation immediately upon the request of the relevant authority, it should be highlighted that a minor variation of Type IA may in specific circumstances be rejected with the consequence that the holder must immediately cease to apply already implemented variations concerned."

By contrast, the former "CMDh best practice guides for the submission and processing of variations in the mutual recognition procedure"[12] states on page 22 in paragraph "Review phase (Day 0–30)":

> "If all the documentation has not been provided, the notification will be deemed unacceptable and the MAH should immediately cease to apply the concerned variation(s) or the MAH may decide to submit a new variation, which will require a new variation procedure number."

[12] CMDh best practice guides for the submission and processing of variations in the mutual recognition procedure (Doc. Ref.: CMDh/094/2003/Rev.19 of February 2013)
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Variations/CMDh_094_2003_Rev.19_2013_03_Clean.pdf
(28.12.2013; archived by WebCite® at http://www.webcitation.org/6MD1CKwbB).

The revised wording in the new, updated Classification Guideline allows the competent authorities to accept amendments of IA variations and prevent resubmissions. This will help to reduce the workload on both, the applicants and the competent authorities side.

2.1.2 Implicit approval of IB variations

The procedural guidance in the updated Classification Guideline describes in detail the implicit approval obtained for IB variations within 30 days following the acknowledgement of receipt of a valid notification for MRP/DCP, CP and purely national procedure (section 2.2.2., 2.2.3. and 2.2.4. for MRP, purely national procedure and CP respectively). The type IB variations review process for the purely national procedure compares to the process for MRP, except that no CMS is involved.

In addition, procedural guidance is given on type II variations and worksharing as well. In this way, information formerly distributed over former Classification Guideline and "CMDh best practice guides for the submission and processing of variations in the mutual recognition procedure"[13] has been combined in the updated Classification Guideline.

2.1.3 Opening clause for type II variations

On page 29 of the updated Classification Guideline, the third paragraph in the introduction of the annex is worded as follows:

> "When several minor changes are taking place (e.g. to the same method or process or material) at the same time or in cases of a major update of the quality information for the active substance or the finished product, the applicant should take into account the overall impact of these changes on the quality, safety or efficacy of the medicinal product when considering the appropriate classification and submit them accordingly. Specific supporting data for Type IB and Type II variations will depend on the specific nature of the change."

This can be considered as an opening clause for type II variations. Instead of updating a module 3 of the dossier with many IA and IB variations in one or more grouped submissions, the applicant could claim that the many minor changes may have a significant overall impact on the quality, safety or efficacy and submit the changes as one variation of type II.

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[13] CMDh best practice guides for the submission and processing of variations in the mutual recognition procedure (Doc. Ref.: CMDh/094/2003/Rev.19 of February 2013)
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Variations/CMDh_094_2003_Rev.19_2013_03_Clean.pdf
(28.12.2013; archived by WebCite® at http://www.webcitation.org/6MD1CKwbB).

In the past, it has already been recommended to submit substantial changes in the updated version of an ASMF as a single type II variation under category B.I.z (question 3.4 in CMDh Q/A-List for the submission of variations[14]).

The same approach is followed in question 4.12 of the same CMDh Q/A-List on module 1 update. The answer recommends using a single type II variation under category C.I.z:

> "In order to conform to the current legislation all changes for the update of Module 1, including changes or addition of Braille, readability user testing, environmental risk assessment, summary of pharmacovigilance system or risk management plan, may be submitted as one single variation of type II under category C.I.z."

In December 2013 the CMDh Q/A-List for the submission of variations was amended with question 4.16 on harmonisation of the quality dossier. Once again, the answer recommends using a type II variation:

> "Applications for the harmonisation of the quality dossier for products not participating in a former Article 30 procedure may also be submitted as type II variations under category B.V.b.1.z."

Consequently, with reference to the overall impact of the changes on the quality, safety or efficacy of the medicinal product, it should now be possible to notify a complete transfer of production site, including consequential adaptions of manufacturing process, test methods, in-process controls, testing frequencies and specifications as one single variation of type II under category B.II.z.

Another example for a "major update of the quality information" is an update of a dossier to current state of scientific and technical progress, including recent process validation reports, stability data and certificates as well as complete switch from the old dossier format (NTA, Vol. 2B; edition 1998) to the current dossier format "EU-CTD" (NTA, Vol. 2B, edition May 2006).

The last sentence of the opening clause also mentions IB variations. Hence, where reasonable, it should be possible to submit several IA variations as one single variation of type IB. One example could be a minor change in the manufacturing process (B.II.b.3), which includes changes in equipment, overages, order of sieving and mixing steps and corrections in the

[14] CMDh: Q/A-List for the submission of variations according to commission regulation (EC) 1234/2008 (Doc. Ref: CMDh/132/2009/Rev.24 of December 2013); http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Questions_Answers/CMDh_132_2009_Rev24_12_2013_clean.pdf (02.02.2014 archived by WebCite® at http://www.webcitation.org/6N5NHoZAI).

batch formula. However, future experiences with the various authorities will still have to confirm this approach.

2.1.4 Handling of editorial changes in the Classification Guideline

For correction of editorial changes there is no own change category in the Classification Guideline. However, in section "4. ANNEX" of the updated Classification Guideline directions are given on how to handle editorial changes:[15]

> "If amendments to the dossier only concern editorial changes, such changes should generally not be submitted as a separate variation, but they can be included in a variation concerning that part of the dossier. In such cases the changes should be clearly identified in the application form as editorial changes and a declaration that the content of the concerned part of the dossier has not been changed by the editorial changes beyond the scope of the variation submitted should be provided. It should be noted that editorial changes include the removal of obsolete or redundant text but not the removal of specification parameters or manufacturing descriptions."

A similar wording had already been contained in the former Classification Guideline[16], but the request to identify the editorial changes in the application form and the definition of editorial changes were missing.

It should be noted positively, firstly that no separate variations are requested for editorial changes and secondly that a definition of editorial changes is given. This is very helpful in practice.

2.1.5 Inclusion of Article 5 recommendations

According to Article 5 of the Variations Regulation, recommendation on the classification can be obtained prior to submission or examination of a variation whose classification is not provided for in the Variations Regulation or Classification Guideline.

In the original version of the Variations Regulation, the MAH could send his request directly to the coordination group (CMD). Since amendment of the Variations Regulation by

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[15] Updated Classification Guideline, page 29, last paragraph (Brussels, 16.05.2013).

[16] Reference is made to page 3, last paragraph in "Communication from the Commission – 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", effective from 01.01.2010 to 03.08.2013; http://ec.europa.eu/health/files/betterreg/pharmacos/classification_guideline_adopted.pdf (27.12.2013, archived by WebCite® at http://www.webcitation.org/6MBee7GYJ).

Commission Regulation (EC) No 712/2012 (this amendment applies since 02.11.2012), the MAH has to request the recommendation on a classification from the competent authority. Competent authorities may still request a recommendation on classification directly from the CMD.

Whilst the former Classification Guideline was effective (from 22.01.2010 to 04.08.2013), by means of Article 5 procedure 47 recommendations on the classification were made public in the list of "CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008" (April 2013).[17]

After the update of the classification guideline on 16.05.2013, the list of "CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008" (July 2013)[18] was reduced to 36 recommendations in total. Eight of the recommendations are dated between June and July 2013 and are not yet present in the list of April 2013; they have to be subtracted to ensure a fair comparison and are listed separately as '+(8)' below:

Table 1: Comparison of the number of Article 5 recommendations April/July 2013

Recommendations on	As per April 2013	As per July 2013
B. Quality changes	35	19
C. Safety, Efficacy, Pharmacovigilance Changes	7	4+(8)
Other proposed changes not relevant for Classification	4	4
Other Changes – Classification to be confirmed	1	1
Total	47	28+(8)

Compared to the list from April 2013 containing 47 recommendations in total, 19 of these Article 5 recommendations were deleted, 16 'B' and 3 'C' recommendations.

When considering the date of the individual recommendations, it can bee seen, that primarily older recommendations were deleted, 13 were from 2010:

[17] List can be provided on request; former link: http://www.hma.eu/293.html (23.04.2013).
[18] http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Variations/Art_5_Recommendations/CMDh_171_2010_2013_07_a.xls
(27.12.2013, archived by WebCite® at http://www.webcitation.org/6MBJqPqju).

Table 2: Dates of deleted Article 5 recommendations

Year	Number of listed recommendations dated from 2010 until April 2013 before update	Number of listed recommendations dated from 2010 until April 2013 after update (July 2013)	Number of deleted recommendations
2010	30	17	13
2011	7	4	3
2012	8	5	3
2013 January-April	2	2	0
Total	47	28	19

This gives rise to the question of which particular recommendations have been deleted and for what reason. For further investigation a list of the 19 deleted recommendations was prepared and the individual recommendations were compared to the updated classification in the Classification Guideline of 16.05.2013.

Some of the deleted recommendations led to addition of new topics in the Classification Guideline, such as “h) Adventitious Agents Safety” that covers five former B.I.z-recommendations.

Other deleted recommendations led to amendments of existing topics, e.g. the topic

> “B.I.d.1 Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier.”

was amended with:

> “c) Change to an approved stability protocol”

So the recommendation “B.I.d.z - Deletion of tests or reduction in the frequency of testing in a previously approved stability protocol of the active substance” from 25.07.2011 was made redundant by the new category “B.I.d.1.c - Change to an approved stability protocol”.

Accordingly, the proposed changes of all deleted recommendations could be classified unambiguously using the updated Classification Guideline of 16.05.2013. For a list of deleted Article 5 recommendations reference is made to Annex 6: List of deleted Article 5 recommendations. Hence, all deleted recommendations were made redundant by the update.

This makes the use of the new, updated Classification Guideline of 2013 easier in practice, as more topics are covered.

2.1.6 Comparison of former and updated classification

Additional variation codes

Compared to the former Classification Guideline, the updated Classification Guideline contains below additional variation codes:

- A.8 Changes to date of the audit to verify GMP compliance of the manufacturer of the active substance
- B.I.e.4 Changes to an approved change management protocol
- B.I.e.5 Implementation of changes foreseen in an approved change management protocol
- B.II.g.4 Changes to an approved change management protocol
- B.II.g.5 Implementation of changes foreseen in an approved change management protocol
- B.II.h Adventitious Agents Safety & B.II.h.1 Update to the "Adventitious Agents Safety Evaluation" information (section 3.2.A.2)
- C.I.10 Change in the frequency and/or date of submission of periodic safety update reports (PSUR) for human medicinal products
- C.I.11 Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan
- C.I.12 Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring
- C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority
- C.II.7 Introduction of a new Pharmacovigilance system
- C.II.8 Change in the frequency and/or date of submission of periodic safety update reports (PSUR)

No additions or amendments were made in section D. PMF/VAMF, besides the changes of "shall" into "must" in D.1, D.2 and D.4 and "EMEA" into "EMA" in D.3 without affecting the meaning.

The addition of categories B.II.h, C.I.10 and C.II.8 resulted from the inclusion of the respective Article 5 recommendations as set out above.

Other additions closed gaps (A.8, B.I.e.4, B.II.g.4, C.I.11-13, C.II.7).
The additions B.I.e.5 and B.II.g.5 are modified versions of the former, deleted topic B.V.c.1.

Compared to the former Classification Guideline, the updated Classification Guideline contains many amendments of already existing categories of change. The amendments include corrections, clarifications, editorial changes, updates of names (e.g. EMEA into EMA) as well as adaption to new legislations.
Additions to the descriptions of changes were made for better understanding of their scope and applicability.

Some amendments are due to former Article 5 recommendations (see Annex 6: List of deleted Article 5 recommendations). Other amendments are based on the authorities' experiences with known troubled spots as well as gaps in the former Classification Guideline. Below amendments should be mentioned with respect to this.

Deletion of a non-significant parameter

One element of uncertainty was the confusion on "deletion of a non-significant parameter". The Medicines and Healthcare products Regulatory Agency (MHRA) has given guidance to this topic already in their "Quality changes FAQs" number 19[19] in the past:

> "It should not be seen as an opportunity to try and delete any possible parameter. Consideration should always be given to the background of why the test was included in the first place and consequently the implication of the deletion, which in most cases will require assessment."

In the spirit of this, the updated Classification Guideline provides a precise definition of 'non-significant' in terms of deletion of tests or parameters from in-process tests or specifications.
New conditions were added to the categories of change defining critical parameters and tests that must not be considered as non-significant (e.g. critical physical characteristics).

For below categories of change new conditions were introduced defining precisely significant tests and parameters using examples:

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[19] MHRA, Variations to licences: Quality changes FAQs, question number 19: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Marketingauthorisations/Variationstolicences/FAQsforvariationssubmittedafter1January2010/Qualitychanges/index.htm#19 (30.12.2013; archived by WebCite® at http://www.webcitation.org/6MFp8zWdT).

Table 3: Categories of change defined more precisely by new conditions

Active substance		New condition no.
B.I.a.4.c	Deletion of a non-significant in-process test	7
B.I.b.1.d	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	8
Finished product		New condition no.
B.II.b.5.c	Deletion of a non-significant in-process test	7
B.II.c.1.c	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	8
B.II.d.1.d	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)	9

For deletion of non-significant parameters of container (B.I.c.2 and B.II.e.2) or measuring or administration device for veterinary medicinal products (B.IV.2) no additional conditions were included.

In the respective sections "Documentation", the requirements for the mandatory justification that has to be submitted along with every deletion of a non-significant parameter were amended with "…or that the parameter is obsolete." This results in a general statement such as "Justification/risk assessment showing that the parameter is non-significant or that the parameter[20] is obsolete." Accordingly, even a significant parameter may be deleted if it becomes obsolete by introduction of other tests or parameters.

Change in batch size (including batch size ranges)

An up to 10-fold increase in batch size of active substance and intermediates (B.I.a.3) or of the finished product (B.II.b.4) is still possible as a variation IA, but now compared to the "originally", and not the "currently" approved batch size as was formerly the case.

This is a more precise definition compared to the former Classification Guideline. The basic principle of not allowing a more than 10-fold increase compared to the last assessed and approved batch size without further assessment had already been followed in the former Classification Guideline, but it was kind of hidden in conditions 7 and 8 of B.II.b.4 and B.I.a.3 respectively: "The currently approved batch size was not approved via a Type IA

[20] Note: In the updated Classification Guideline the requirements for the mandatory justification mention by error "in-process parameter" in categories B.I.b.1.c (control of active substance) and B.I.c.2.c (container of active substance) were it should read "specification parameter").

variation". Additionally, for the active substance, downscaling of the batch size via IA variation is now limited to 10-fold.

Changes to the quality dossier requested by the competent authority

The table of contents of the annex of the updated Classification Guideline lists under point

> B. QUALITY CHANGES
> V. Changes to a marketing authorisation resulting from other regulatory procedures

The topic

> c) Other changes to the quality dossier requested by the competent authority (formerly: "c) change management protocol", now available under "B.I.e.5" and "B.II.g.5" - Implementation of changes foreseen in an approved change management protocol).

Later in the annex, there is no further mention of a category "B.V.c)". The former category "B.V.c) change management protocol" was revised and included under. "B.I.e.5" (active substance) and "B.II.g.5" (finished product). There is no mention of a "B.V.c)" category in the updated variation application form, too.[21] Hence, it remained unclear whether a variation "B.V.c)" could be used, e.g. for fulfilment of sanctions or whether the topic "c) Other changes to the quality dossier requested by the competent authority" is just an editorial error.

For clarification a request was sent to the BfArM in January 2014 and the response points out, that fulfilment of sanctions and official requirements have to be submitted using the appropriate change categories of the Classification Guideline. The presence of "c) Other changes to the quality dossier requested by the competent authority" in the table of contents is considered as an error in the word-document (Annex 1: Request to BfArM on category "B.V.c" of the Classification Guideline).

Implementation of the outcome of a Union referral procedure

The description and conditions of the two change categories applicable to implement the outcome of a Union referral procedure (e.g. as defined by Article 30 or 31 of Directive 2001/83/EC) have been simplified and clearly arranged:

> "B.V.b.1 Update of the quality dossier intended to implement the outcome of a Union referral procedure"

[21] Application form for variation to a marketing authorisation for medicinal products (human and veterinary) to be used in the mutual recognition and the centralised procedure. (July 2013) http://ec.europa.eu/health/files/eudralex/vol-2/c/variation_form__201307_en.pdf (29.12.2013; and archived by WebCite® at http://www.webcitation.org/6ME2aanmS).

"C.I.1 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure
No change in variation type"

Examples for closed gaps by new subitems

Examples for closed gaps in addition to included Article 5 recommendations can be found in:

"B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate …",

new subitems g, i-k (subitem h is based on an Article 5 recommendation, please see above).

"B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance…
i) Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the active substance, a change in specification from in-house to a non- official Pharmacopoeia or a Pharmacopoeia of a third country"

Hereby a variation IB was introduced for a change in specification from in-house to non-official Pharmacopoeia or third country Pharmacopoeia, on condition that the change does not concern control of a genotoxic impurity.

"B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product …
b) Replacement or addition of a site where batch control/testing takes place for a biological/immunological product and any of the test methods performed at the site is a biological/immunological method"

This variation is now clearly defined as a variation type II.

"B.II.d.2 Change in test procedure for the finished product…" contains now the new subitems e) and f) for adaption to updated Ph. Eur. and "to reflect compliance with the Ph. Eur. …". Subitem f) allows as well the removal of outdated references.

"B.II.e.1 Change in immediate packaging of the finished product" – a new subitem was added for clarification (no deletion of a complete strength possible), along with specific conditions, that remaining pack sizes must be consistent with dosage regimen:

"b)3. Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form"

"B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability" – there are new subitems "a)4" and "b)4" for deletion of certificates by variation IA.

In addition there is the new subitem "a)5" for submission of a new Certificate of Suitability to the relevant Ph. Eur. Monograph (CEP) for a non-sterile active substance that is to be used in a sterile medicinal product (requires a IB variation).

Eventually there is the new subitem “b)5” requesting a variation type II for submission of a

> “New/updated (TSE) certificate from an already- approved/new manufacturer using materials of human or animal origin for which an assessment of the risk with respect to potential contamination with adventitious agents is required”.

> “C.II.6 Changes to the labelling or the package leaflet which are not connected with the summary of product characteristics”

The new subitem “a)” defines that “Administrative information concerning the holder's representative” is an IAIN, whereas all other changes remain an IB variation. Consequently, now purely administrative information can be submitted without assessment and hence a gap was closed.

Changes in the assigned procedure type

Based on more experience or new legislation some changes in the procedure type were made in the updated Classification Guideline:

> “C.I.3 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006”

Implementation of wording already agreed by the competent authority is now accepted as IAIN (formerly IB) on condition that it does not require the submission of additional information and/or further assessment.

> “C.I.8 Introduction of, or changes to, a new summary of pharmacovigilance system for medicinal products for human use”

Due to the new pharmacovigilance legislation and the switch from a Detailed Description of the Pharmacovigilance System (DDPS) to Pharmacovigilance System Master File (PSMF) the procedure type changed from formerly type II and IB to IAIN for summary of PSMF introduction or changes in QPPV or PSMF.

> “C.II.6 Changes to the labelling or the package leaflet which are not connected with the summary of product characteristics”

As already mentioned above, the subitem a) defines that “Administrative information concerning the holder's representative” is an IAIN, whereas all other changes remain an IB variation.

"B.I.b.2 Change in test procedure for active substance or starting material/reagent/ intermediate used in the manufacturing process of the active substance

d) **Substantial** change to or replacement of a biological/ immunological/ immunochemical test method or a method using a biological reagent for a biological active substance"

It is still a type II variation but "substantial" was added, so in connection with modified sub-item "a) Minor changes to an approved test procedure", a minor change can now be submitted under subitem a) for a minor change in biological/ immunological/ immunochemical test method as a variation IB (condition 4 is not fulfilled hence no IA variation).

2.2 Implication of the Variations Regulation for national MAs

2.2.1 Features of the former national German variation system

The former national German variation system worked with change items that were coded by structural numbers (SKNR). Considering module 3 of the dossier, none of the change items required prior approval, except for changes in the composition. Moreover, all notifications of change that did not require approval, worked as simple "tell and do" submissions with no need to wait for a positive validation. The absence of a validation phase was an important feature, as for European variation procedures it has been reported that the validation phase is routinely exceeded in the experience of the applicant.[22]

For change items that required prior approval, submission followed the "tell, wait and do" scheme, with no need to wait for confirmation of a successful validation. In case no feedback was received from the competent authority within 3 months after submission, the notification of change was considered accepted (principle of implicit approval).

Eventually, in one notification of change different change items could be grouped without limitations.[23]

This lean system with predictable timelines was supported by the easy electronic submission via upload in the PharmNet.Bund portal. Even after the „Zweites Gesetz zur Änderung

[22] For more details please refer to: Dr. Verena Tautorat, DGRA master thesis, "The end of an era: Implementing Variation Directive 2009/53/EC into German Drug Law", Bonn, 2011, page 21, http://dgra.de/media/pdf/studium/masterthesis/master_tautorat_v.pdf (15.02.2014; archived by WebCite® at http://www.webcitation.org/6NP0iItiR).

[23] For more details please refer to: Dr. Verena Tautorat, DGRA master thesis, "The end of an era: Implementing Variation Directive 2009/53/EC into German Drug Law", Bonn, 2011, page 20, http://dgra.de/media/pdf/studium/masterthesis/master_tautorat_v.pdf (15.02.2014; archived by WebCite® at http://www.webcitation.org/6NP0iItiR).

arzneimittelrechtlicher und anderer Vorschriften“ of 19.10.2012 (‘16. AMG-Novelle’) had become effective and the list of change items/SKNRs had been harmonised[24] with the change categories in the Classification Guideline, the handling of notifications of change was still easier compared to variations.

2.2.2 Comparison of Section 29 AMG with Chapter IIa of the Variations Regulation

Please find below a summary of the features of the national German variation system compared with the system of the Variations Regulation:

Table 4: Comparison of Section 29 AMG with Chapter IIa of the Variations Regulation [25]

National German variation system	**The Variations Regulation**	
grouping not limited	grouping limited	
Default is notification of change according Section 29(1) AMG	Type IB variation by default	
Without prior approval		
notification of change according Section 29(1) AMG “tell and do” and Section 29(2b) AMG “do and tell”)	IA Variation (“do and tell”)	
no validation	30 days validation phase	
no fixed handling time	30 days after start of validation	
no approval procedure	submission must be valid	
With prior approval		
notification of change according Section 29(2a) AMG	IB variation	Type II variation
no validation	7 days	14 days
implicit approval 90 days upon receipt of the notification	30 days handling time, implicit approval 30 days after start of the procedure	30, 60 or 90 days handling time (plus clock stop), no implicit approval

[24] Gemeinsame Bekanntmachung des Bundesinstituts für Arzneimittel und Medizinprodukte (BfArM) und des Bundesamtes für Verbraucherschutz und Lebensmittelsicherheit (BVL) über die Änderungen des § 29 Absatz 2a Nummer 4 AMG und zum neu eingefügten § 29 Absatz 2b AMG durch das Zweite Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften vom 19. Oktober 2012 (BGBl. I S. 2192), Bonn, 14.01.2013, BAnz AT 31.01.2013 B5, http://www.bfarm.de/SharedDocs/Bekanntmachungen/DE/Arzneimittel/aender/bm-aender-aenderungPar29-pdf.pdf?__blob=publicationFile&v=3 (12.02.2014; archived by WebCite® at http://www.webcitation.org/6NOzYX9R3).

[25] The comparison was adapted from Mariela Becker, “Umsetzung der Variation Regulation für rein nationale Zulassungen“, BfArM im Dialog, 12.07.2013, http://www.bfarm.de/SharedDocs/Downloads/DE/Service/Termine-und-Veranstaltungen/dialogveranstaltungen/dialog_2013/130712/02_Becker.pdf?__blob=publicationFile&v=1 (19.01.2014; archived by WebCite® at: http://www.webcitation.org/6Mk97IcRC).

One more difference between Section 29 AMG and the Variations Regulation should be mentioned as discussed in the master thesis of Dr. Verena Tautorat from 2011:[26]

> "Nationally, it is possible to change the pharmaceutical form into a comparable one by way of a change application requiring prior approval. But it would require the submission of a new MAA in case an indication outside the currently approved area of therapy is applied for. The exact opposite is the case when consulting the Variations Regulation."

With the inclusion of the purely national MAs in the scope of the Variations Regulation this unequal treatment ended, as Section 29(2a) and (3) AMG are no more applicable for MAs that fall under the scope of the Variations Regulation according to Section 29(5) AMG.
The difference holds only meaning for the purely national MAs that are still excepted from the scope of the Variations Regulation.

2.2.3 Former list of change items

The former list of change items in the national German variation System was quite comprehensive and some of the change items have no counterpart in the Classification Guideline, for example:

SKNR 1883	Results of stability testing of finished product without change in shelf life
SKNR 4248	Adaption of texts to QRD-Template according to Version 8 Rev. 2011
SKNR 1211	Fulfilment of conditions (in German: Auflagenerfüllung)
SKNR 1763	Editorial change (in German: redaktionelle Änderung; used to make changes in the labelling)
SKNR 1331	non-official part of the labelling (in German: nicht amtlicher Teil der Informationstexte)

With Variations Regulation becoming effective for purely national MAs, such useful change items were abandoned. By means of unforeseen IB variations such changes can be submitted in the European Variation system too, but at significant higher cost and effort.

2.2.4 National peculiarities that are not under the scope of the Variations Regulation

A few change items are still outside of the scope of the Variations Regulation and the obligation to notify pursuant to Section 29(1) AMG applies for them:

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[26] Dr. Verena Tautorat, MDRA master thesis, "The end of an era: Implementing Variation Directive 2009/53/EC into German Drug Law", Bonn, 2011, page 40, http://dgra.de/media/pdf/studium/masterthesis/master_tautorat_v.pdf (15.02.2014; archived by WebCite® at http://www.webcitation.org/6NP0iItiR).

- Change in ownership (transfer of a MA to a different legal entity)[27]
- After expiry of the usage patent[28], the indication has to be included on a national level only, as it is already available in the harmonised SmPC.
- Changes to the content of the 'blue box' information[29]
- New pack size for German market, that has already been mentioned in the harmonised SmPC
- Hospital bundle pack size (when base size has already been part of the harmonised SmPC)
- Change in sample pack size[30]
- Co-promotion
- Change in local representative
- Change in legal category[31]

2.2.5 Adaptions of BfArM for purely national MA due to the switch to the Variations Regulation

Procedure number

For German purely national MAs there is no procedure number combining the different strengths of a medicinal product in one procedure as in MRP/DCP. Each strength represents an own MA with an individual national MA-number and national submission number (ENR). Hence, for submission of a national variation, a procedure number has to be created to combine the different strengths in one variation. This collective submission (in German: Sammelanzeige) was enabled by introduction of Article 13d(2)(c) in the Variations Regulation through Commission Regulation (EU) No 712/2012 of 3 August 2012. The

[27] Article 1(2) of Commission Regulation (EC) No 1234/2008 excludes transfers of a marketing authorisation from one marketing authorisation holder to another from its scope.
[28] Patents are not harmonised, as there is no "European Patent" yet. Hence, according to Article 11 of Directive 2001/83/EC, "For authorisations under Article 10, those parts of the summary of product characteristics of the reference medicinal product referring to indications or dosage forms which were still covered by patent law at the time when a generic medicine was marketed need not be included." Consequently, the patented indication can be omitted in the national texts.
[29] According to the CMDh Standard Operating Procedure for Article 61(3) changes (CMDh/098/2005/Rev3, October 2011), p. 1, under scope: "Changes to information agreed on a national basis, for example the content of the 'blue box' information, or changes resulting from a translation issue, are outside the scope of this procedure and should be agreed with the Member States concerned according to national procedures".
[30] Study documentation MDRA-15, Modul 5 - Dr. Peter Bachmann, Part 2, pages 46, 50-64.
[31] Co-promotion, local representative, legal category are listed as change of "…Mitvertreiber, örtlicher Vertreter, Verkaufsabrenzung" in the presentation of Mariela Becker, "Umsetzung der Variation Regulation für rein nationale Zulassungen", BfArM im Dialog, 12.07.2013, http://www.bfarm.de/SharedDocs/Downloads/DE/Service/Termine-und-Veranstaltungen/dialogveranstaltungen/dialog_2013/130712/02_Becker.pdf?__blob=publicationFile&v=1 (19.01.2014; archived by WebCite® at: http://www.webcitation.org/6Mk97IcRC).

collective submission can be combined with additional grouping, as long as the various changes affect all medicinal products in the collective submission.

As per current communication of the BfArM[32], the procedure number has to be created using the highest procedure type of the submission (IA/IB/II), the ENR of the purely national MA, submission date (YYYYMMDD) and a sequential number starting with "01" for first submission for this MA on this day (e.g. IB-2154321-20131124-01). To combine more than one strength in the submission (e.g. ENR 2154321-2154323), a specifier ("S" for "Sammelanzeige") has to be included and the smallest ENR has to be used (e.g. IB-S-2154321-20131124-01). This is a very pragmatic approach and the procedure numbers can be assigned easily without need to investigate the submission history.

Generous grouping

With reference to Article 13d(2)(c) of the amended Variations Regulation (Commission Regulation (EC) No 1234/2008 of 24 November 2008 as amended by Commission Regulation (EU) No 712/2012 of 3 August 2012, effective since 4 August 2013), the BfArM allows in general below grouping of change items for purely national MAs:[33]

Administrative changes as listed in chapter A of the Classification Guideline may be grouped with quality changes as listed in chapter B of the Classification Guideline.

Administrative changes as listed in chapter A of the Classification Guideline may be grouped with safety, efficacy and pharmacovigilance changes as listed in chapter C of the Classification Guideline.

The combination of changes of chapters B and C of the Classification Guideline will be not accepted unless the changes are directly dependent on each other.

[32] Bekanntmachung über die Anzeige von Variations für rein nationale Zulassungen gemäß Kapitel IIa der Verordnung (EG) Nr. 1234/2008 ab dem 04.08.2013, die gemäß § 77 AMG in die Zuständigkeit des BfArM fallen vom 12. Juli 2013, Bonn 12.07.2013, http://www.bfarm.de/SharedDocs/Bekanntmachungen/DE/Arzneimittel/aender/bm-aender-20130712-Anzeige.pdf?__blob=publicationFile&v=4 (19.01.2014; archived by WebCite® at http://www.webcitation.org/6Mk7Xo8Gj).

[33] Bekanntmachung über die Anzeige von Variations für rein nationale Zulassungen gemäß Kapitel IIa der Verordnung (EG) Nr. 1234/2008 ab dem 04.08.2013, die gemäß § 77 AMG in die Zuständigkeit des BfArM fallen vom 12. Juli 2013 (19.01.2014; archived by WebCite® at http://www.webcitation.org/6Mk7Xo8Gj).

By these three simple rules, grouping of national variations is remarkably facilitated, unless they do not limit the grouping of solely IA variations. This should not be the case as according to Article 13d(2)(a) of the amended Variations Regulation, all IA variations may be grouped: "…a single notification as referred to in Article 13a may cover all such variations;"
Confirmation is given in paragraph 2.1.1. of the Classification Guideline, that

> "the holder may group one or more minor variations of Type IA to the terms of several marketing authorisations under a single notification provided that the variations are the same for all marketing authorisations concerned and they are notified at the same time to the same relevant authority."

Experience from first submissions in September 2013 indicated that the combination of not related variations of chapters B and C of the Classification Guideline was not accepted even in case of grouping solely IA variations.[34]
Upon enquiry in January 2014, the BfArM confirmed that there are no restrictions to certain chapters for grouped applications that contain only IA variations. The restriction for grouping of changes of chapters B and C of the Classification Guideline has only to be considered if IB or type II variations are included in the group. A respective clarification of the BfArM is in preparation (Annex 2: Request to BfArM on grouping of IA variations).

Status mails

For national variations there will be no official approval mails, instead the system of status mails sent by PharmNet.Bund has been refined.[35] Only in case of invalidation and rejection of a national variation a separate notice will be sent to the applicant. Otherwise the status mails will be legally binding. Recently (January 2014) it has been noted, that the status mails on positive closure are send with a delay.[36]

PharmNet.Bund portal

The PharmNet.Bund portal[37] has been adapted accordingly and is now capable to manage submission of variations, national variations and notifications of change. Submission via the PharmNet.Bund portal is supported by the Common European Submission Platform (CESP). CESP can be used to upload high volumes of data that can be linked to the submission made

[34] BfArM, Division licensing, Simplified procedures I, personal and e-mail communication (15.10.2013).
[35] Bekanntmachung über die Anzeige von Variations für rein nationale Zulassungen gemäß Kapitel IIa der Verordnung (EG) Nr. 1234/2008 ab dem 04.08.2013, die gemäß § 77 AMG in die Zuständigkeit des BfArM fallen vom 12. Juli 2013 (19.01.2014; archived by WebCite® at http://www.webcitation.org/6Mk7Xo8Gj).
[36] betapharm Arzneimittel GmbH, regulatory affairs department, personal communication (17.01.2014).
[37] PharmNet.Bund: German Institute of Medical Documentation and Information, the Drug Information Portal of the Bund (Federal Government) and the Laender (States), http://www.pharmnet-bund.de (24.09.2013).

in the PharmNet.Bund portal. CESP is necessary as the number of uploads is limited in PharmNet.Bund portal. Alternatively different files (e.g. highlighted versions of texts) can be merged in one PDF-file but this increases the workload on both sides.

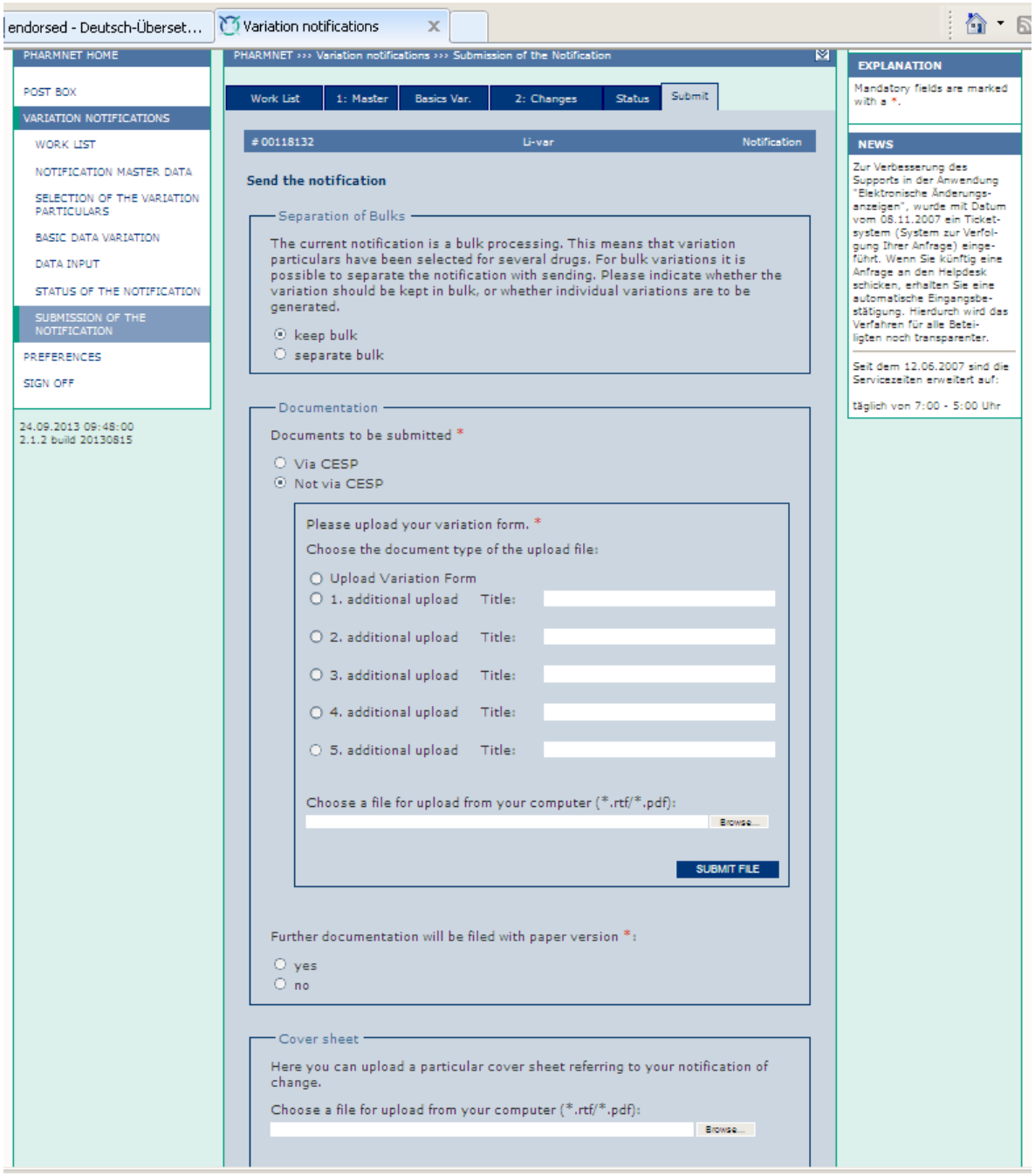

Figure 1: Screenshot of PharmNet.Bund portal's online variation submission section for uploads showing limitation to six files.[38]

[38] PharmNet.Bund portal, the Drug Information Portal of the Bund (Federal Government) and the Laender (States), screenshot of the section for uploads showing limitation to six files, https://anwendungen.pharmnet-bund.de/e-AeA/servlet/FlowController/UpdateAndGetNextPage#__DEFANCHOR__ (24.09.2013).

Adaption of the fees

At present, the calculation of the fees for national variations is still provisional, as the fees are subject to subsequent review. The BfArM expressly reserves the right to charge the correct fees after amendment of the AMG Fees Ordinance (AMGKostV). The exact fee rates are expected to range between the German RMS- and CMS-fees for variations.[39]

In January 2014 a first non-public draft of the AMGKostV of the BMG was circulated.[40] In terms of national variations the proposed fees are in the range of the previous fees for notifications of change according to Section 29 AMG. Moreover, the proposed fee rates range between the German RMS- and CMS-fees for variations.

2.3 Borderline cases in the application of the Variations Regulation

2.3.1 National variation for a German MA within an MRP/DCP

Variations to MRP/DCP MAs have to be submitted according to the Variations Regulation, as long as the harmonised parts of the MAs are concerned. Additionally, the so-called 'non-variations' have to be submitted according to Article 61(3) of Directive 2001/83/EC for changes of labelling or the package leaflet that are not connected with the SmPC.

Yet, there are few change items that do not concern the harmonised position, but only single national MAs within the MRP/DCP, such as already listed in section 2.2.4 (Change in ownership, expiry of the usage patent, new pack size for German market, that has already been mentioned in the harmonised SmPC, et cetera).

These change items are outside of the scope of the Variations Regulation too and consequently the obligation to notify pursuant to Section 29(1) AMG applies for them in Germany.

Nevertheless, submission of a national variation was demanded by the BfArM for a new pack size for the German market already mentioned in the harmonised SmPC.[41] So instead of using the DCP-number, a procedure number had to be created using the ENR of the affected MA and a national variation of the category B.II.e.5.a had to be submitted.

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[39] BfArM, FAQ Variations, former link: http://www.bfarm.de/DE/Service/FAQ/_functions/Amzul/aender/variareg/C_gebuehren/variareg_C_table_gesamtansicht.html?nn=4287354 (19.01.2014 archived by WebCite® at http://www.webcitation.org/6Mk6qRYVo).

[40] BMG, AMGKostV, non-public draft of 30.01.2014, personal e-mail communication of Bundesverband der Arzneimittel-Hersteller e.V., (31.01.2014).

[41] BfArM, Division licensing, Simplified procedures I, personal communication (05.09.2013).

Basically, inclusion of an already approved pack size in the German texts is not an addition of a pack size but only a change in the national texts and should be notified as such. Meanwhile, a statement supporting this view is available in the FAQ-section on the BfArM homepage.[42] Contrastingly, the BfArM's current List of change items as per 08.11.2013 still mentions MRP/DCP under SKNR 0102 (Pack size).[43] This indicates that the internal coordination at BfArM is still ongoing.

By contrast to changes in the pack size, other changes of the list in section 2.2.4, like transfer of MA to a different legal entity, still have to be submitted using a traditional notification of change (in German: Änderungsanzeige). The changes in pack size are different to the other changes in the list in that they have a counterpart in the Classification Guideline (category B.II.e.5.a), even though this category is meant for pack sizes concerning a MRP/DCP and not single national MAs within the MRP/DCP.

2.3.2 Handling of Graduated Plans

Another borderline case is the handling of Graduated Plans: Each Graduated Plan has its own SKNR and it has to be indicated in the application form of national variations under "scope" for purely national MAs. National variations that only serve the purpose to adapt the texts to a Graduated Plan will be free of charge.[44]

The reasoning behind is that the Graduated Plan has already changed all affected purely national MAs and the national variation (category C.I.z, type IA, according to Article 5 recommendation of 29.07.2013) is just regarded as the confirmation of the MAH that he has adapted his texts and labelling accordingly.

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[42] http://www.bfarm.de/SharedDocs/FAQs/DE/Arzneimittel/packungsgroessen/aa_FAQ03.html?nn=3863448 (15.02.2014; ; archived by WebCite® at http://www.webcitation.org/6NP9OceHQ).

[43] BfArM's list of change items, version 1.8 as per 08.11.2013 http://www.bfarm.de/SharedDocs/Formulare/DE/Arzneimittel/Zulassung/aender/Katalogder%C3%84nderungstatbest%C3%A4ndeV18.pdf?__blob=publicationFile&v=3 (25.01.2014 archived by WebCite® at http://www.webcitation.org/6MtGhWuof).

[44] BfArM, Division licensing, Simplified procedures I, personal communication (15.10.2013).

2.3.3 Changes in the non-official part of the labelling

The Variations Regulation does not cover the so-called 'non-variations'. This

> "… changes to an aspect of the labelling or the package leaflet […] and not connected with the summary of product characteristics"[45]

do not fall under the scope of the Variations Regulation but have to be submitted according to Article 61(3) of Directive 2001/83/EC for MRP/DCP.

In case of MRP/DCP, where a harmonised position is to be maintained, the changes in labelling or PL outside of the SmPC can be submitted via the procedure defined in Article 61(3) of Directive 2001/83/EC.[46] A directive has to be transposed into national law and the transposition of Directive 2001/83/EC in the German law is to be found in the AMG.
Consequently, 'non-variations' for purely national MAs still have to be submitted by means of a national notification of change according to Section 29(1) AMG. It should be noted that Section 29(5) AMG suspends Section 29 (2a) and Section 29 (3) but not Section 29(1) AMG for MAs that are under the scope of the Variations Regulation.

Nevertheless, upon request in November 2013, a change in the non-official part of the labelling (additional brief description for opening of blister) had to be submitted as a non-variation according to Article 61(3) of Directive 2001/83/EC for a purely national MA.[47] The notification form had to be modified accordingly as it is not intended for purely national MAs.

For clarification, a request containing above rationale was send to the BfArM in February 2014. No final response was received yet, but it was indicated that the topic is still under discussion.[48]

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[45] Article 61(3) of Directive 2001/83/EC, 06.11.2001, OJ No L 311/87 of 28.11.2001.
[46] CMDh Standard Operating Procedure, Procedure for Article 61(3) Changes to Patient Information, Doc. Ref.: CMDh/098/2005/Rev3, October 2011.
http://www.lakemedelsverket.se/upload/foretag/humanlakemedel/CMDh-098-2005_2011_10_Rev3-Clean.pdf (12.02.2014; archived by WebCite® at http://www.webcitation.org/6NLA3vhhV).
[47] betapharm Arzneimittel GmbH, regulatory affairs department, submission of 21.11.2013, personal communication (14.01.2014).
[48] BfArM, Division licensing, Simplified procedures II, personal communication (14.02.2014).

2.4 Results of the survey

Based on the differences found between former and updated Classification Guideline and based on the implication of the Variations Regulation for national MAs, potential consequences in practice were drawn up and several assumptions and hypotheses were developed.

Furthermore, by contrast to MRP/DCP, no other countries are involved in variations to purely national MAs. This gave rise to the question, whether the authorities might handle national variations differently, for example in terms of priority and complaisance.

The main hypotheses were:

- The new, updated Classification Guideline of 16.05.2013 has an improved and comprehensive catalogue of variation types
- Submissions in the former national German variation system and the intermediate national German variation system were faster and easier compared to the Variations Regulation.
- Fees of the former national German variation system were significantly lower than the fees for variations. Hence, inclusion of purely national MAs in the scope of the Variations Regulation will render many purely national MAs unprofitable and lead to withdrawals.
- It is more difficult and expensive to maintain dossiers at the current state of scientific and technical progress using the Variations Regulation.
- Agencies may handle national variations at a lower priority than variations in MRP/DCP or CP as no other countries are involved.
- Agencies are more complaisant if no CMS is involved
- Agencies are inclined to miss deadlines if no CMS are involved
- The national variations under the scope of the Variations Regulation might develop into a second national system due to the adaptions and national peculiarities like creation of procedure number and different importance of status mails.

To investigate the hypotheses, a questionnaire was created to gather feedback and opinions on the national variations after inclusion of German purely national MAs in the scope of the

Variations Regulation and on advantages and disadvantages of the new or altered classifications of variations.

The questionnaire concentrated on four major topics:

- Differences between former and updated Classification Guideline
- Differences between updated Classification Guideline and former national German variation system
- Management of the transition
- Differences between variations to MRP/DCP and purely national MAs

In the questionnaire, participants were asked to compare the German purely national variations to the former national German variation system, valid until October 2012.
The questionnaire contained open questions to get uninfluenced opinions as well as worded statements, that could be rated from “1” for “I do not agree” to “5” for “I fully agree”. A copy of the questionnaire is attached in Annex 4: Questionnaire of the survey.

With the help of Dr. Jasmin Fahnenstich, M.D.R.A. board of examiners, the survey was sent by e-mail to approximately 300 current and former M.D.R.A. students in December 2013.

Feedback was received from only 14 participants. Hence, a statistical evaluation of the results is not possible. As feedback has been obtained from 14 different companies (two participants are employed by the same consultant but work for different customers) of different sizes (including originators, generic companies and consultants), it will nevertheless substantiate the hypotheses.

A list containing the results of the survey is attached in Annex 5: Tabulation of the survey outcome. On request, the original returned questionnaires could be provided.

The results of the survey are summarized below in the order of question 1 to 24. In case of the open questions multiple answers were possible. Similar answers were grouped for better clarity.

2.4.1 Differences between former and updated Classification Guideline

1. What did you expect from the updated Classification Guideline of 2013?

Table 5: Summary of the responses to question 1 on expectations

Responses	Total votes
Harmonisation of requirements for purely national MAs in the EU	5
Improved and comprehensive catalogue of variation categories	4
Clarification on missing categories and closing of gaps	2
Inclusion of Article 5 recommendations	1
More precise definitions	1
Faster approval of variations in those countries which had not implemented the European variation system yet	1
Simplification of the variation procedures	1
Own IA variation for editorial changes /dossier updates	1
Reintroduction of the Umbrella Type II Variation	1
No expectations / not much / no entry	3

Evaluation

The main expectation was completion of the catalogue of change categories and closing of gaps. As the inclusion of Article 5 recommendations falls under the same topic, this makes a total of 7 responses. The second most frequent answer was harmonisation of requirements.

2. What are your first experiences with the updated Classification Guideline for MRP/DCP/CP Marketing Authorisations (MA) (Advantages, Disadvantages, Problems)?

Table 6: Summary of the responses to question 2 on first experiences

Responses	Total votes
Some gaps in categorisation are closed but not all of them	4
There are more classified changes now.	2
No dramatic changes, except some additional conditions.	1
No relevant differences	1
No problems so far	1
No experience / not applicable / no entry	3

In addition, one answer was given, that rather belongs to question 5:

"There is often a delay (for weeks) of the official validation time before starting the variation procedures of Type IB and Type II. The consequence is an extension of the complete variation procedures."

One further answer was given to question 2, but it was evaluated under question 3 were the answer belongs:

"Good Experience with Variations. We have a lot of national MAs for the same Product. Reduction of time for us."

Evaluation

Six of the answers indicate that the main expectation, completion of the catalogue of change categories, was at least partially met.

3. What are your first experiences with the updated Classification Guideline for use on German purely national MAs (Advantages, Disadvantages, Problems)?

Table 7: Summary of the responses to question 3 on first experiences with German national variations

Responses	Total votes
Harmonised, common system for national and MRP/DCP is an advantage	3
Clear classification/clear requirements	3
Higher costs in comparison to national German variation system	2
No experience or not applicable	3
No problems	2
More administrative work	2
Timelines clearly indicated (Day 0, 30, 60, 90)	1
National peculiarities are still not harmonised, such as the pack sizes, all should be mentioned within the standard sentence for pack sizes in the texts.	1
Disadvantage: submission of several, unconnected changes is more complicated than before.	1
More documents needed for submission - may lead to delays.	1
Disadvantage: less flexibility in Germany, but flexibility was already finished after the change of the German law before.	1
More time consuming, more complex.	1

In addition, three answers given to question 4 and one given to question 2 were evaluated under question 3 were these answers belong:

Table 8: Summary of the responses to question 4 and 2 belonging to question 3

Responses	Total votes
Harmonized and faster approval of variations which therefore can be implemented faster[49]	1
All IAIN that are now also applicable to national procedures (already considered in table 7 under "Harmonised, common system for national and MRP/DCP is an advantage")	(1)
Much less work, because of the fact that for all countries the same package of necessary documents can be prepared. (summarised with the answer that was originally given to question 2: "Good Experience with Variations. We have a lot of national MAs for the same Product. Reduction of time for us.")	2

Evaluation

To work with a harmonised, common system for national and MRP/DCP is seen as an advantage. It is appreciated to have clear requirements for each change. Harmonisation of requirements and time lines saves a lot of work when companies maintain several purely national MAs for the same medicinal product in different member states.

In the other scenario, where a company maintains many purely national MAs for different medicinal products in Germany, the benefits of harmonisation do not take effect. In this scenario the maintenance of purely national MAs has become more expensive, time consuming and complex.

Bearing in mind the two different scenarios, the contrasting responses given can be explained.

4. What changes in classification are of advantage for you (e.g. graduated plans)?

Two participants entered 'Not applicable', one made no entry. Two responded that they have not discovered any advantages yet. Three answers were evaluated under question 3 where they belong to, see above. The other participants gave following individual answers to this question:

- Some gaps in categorisation are closed
- Precise information on Ph. Eur. Updates
- More precise information about RMP-Updates
- Classification is now easier

[49] The wording "Harmonized […] approval of variations" and mentioning of implementation indicate that national variations to several purely national MAs for the same medicinal product are meant.

- Some changes are new and useful (e.g. Ph. Eur. 2.9.40 to replace 2.9.5 or 2.9.6)
- It is clear which documents have to [be] submitted. At least for type IA and IB (the participant mentioned this in question 3 too and the answer was evaluated there.)
- According to EU regulations treatments for human diseases this had to be classified.
- Graduated plans are now IA
- No experiences yet

Evaluation

The answers show that the updated Classification Guideline has an improved and comprehensive catalogue of variation types and the amendments are appreciated. Nevertheless, there seems to be still some room for improvement. Improvements contained in the procedural guidance on the handling of variations are not mentioned in the responses.

5. The updated Classification Guideline stresses again the 7-day validation time for IB variations, only to be extended by 7 more days in case RMS desires upgrade from IB to type II and CMS are given this additional 7 days to agree/disagree. Do the agencies stick to this 7+7 days timeline?

Table 9: Summary of the responses to question 5 on observance of the validation timeline

Responses	Total votes
Yes	3
Yes for RMS DE, no for RMS PT	1
For purely national MAs: depends on the agency (e.g. HU yes, PL no).	1
“No Information”, “no experiences” or “not applicable”	8
CP: timelines are always followed very strict.	1

In this context, one individual answer given to question 2 should be mentioned in this section:

> “There is often a delay (for weeks) of the official validation time before starting the variation procedures of Type IB and Type II. The consequence is an extension of the complete variation procedures.”

Evaluation

Only few answers were obtained to this question. Two participants identified authorities that do not stick to the timeline (Portugal and Poland). According to four participants the deadlines are met.

6. For IB variations "The holder must wait a period of 30 days to ensure that the notification is deemed acceptable by the relevant authorities before implementing the change ("Tell, Wait and Do" procedure). Does this really work or do you wait for official approval of the RMS or national competent Agency?

Table 10: Summary of the responses to question 6 on implicit approval for IB variations

Responses	Total votes
We are implementing after 30 days but there is still a uncertainty.	1
Normally we do not wait for official approval, but some customer do.	1
No, we always wait for official approval of the NCA or of the RMS.	2
We wait for official approval to be on the safe side in case of release relevant variations.	1
No entry, "No Information" or "not applicable"	4
It depends on the country. In the western European countries we wait until the period of 30 days are over and then implement, if there are no questions from the agency, in the eastern European countries we mostly wait until the official approval is given by the authority or we ask the affiliate if we can implement the change.	1
Yes it works.	2
The experience shows: Most time it works, sometimes minor delays are possible.	1
For purely national MAs: depends on the agency (e.g. HU yes, PL no). Note: the same participant gave the same answer under question 5, too.	1

In summary, 5 participants use the implicit approval of IB-variations.

Two of them use it with limitations (uncertainty, customers).

Five participants do not rely on the implicit approval of IB-variations:

Two participants always wait for official approval.

Two other participants make the decision dependent on the RMS.

One participant waits for approval in case the variation affects batch release.

Evaluation

The procedural guidance in the updated Classification Guideline describes in detail the implicit approval obtained for IB variations within 30 days. Thus, a certain level of confidence in this procedure was expected. However, the responses revealed that there is still an uncertainty connected with the implicit approval. This might be based on different experience with the various authorities.

7. Did you already or do you intend to use worksharing for any of your MRP/DCP MAs?

Table 11: Summary of the responses to question 7 on usage of worksharing for MRP/DCP MAs

Responses	Total votes
Yes	2
No	8
Not yet, maybe in future.	1
Not applicable	2
Abstention/no entry	1

Evaluation

Worksharing is not used very frequently, only two of the participants have used it already. One participant indicated that he might use it in future. One applicant stated that worksharing was not applicable, as they have almost only purely national MAs.

8. Did you already or do you intend to use worksharing for any of your purely national MAs? If yes, please indicate your motivation and planned amount of national worksharing submissions. If no, please indicate your motivation.

Table 12: Summary of the responses to question 8 on usage of worksharing for purely national MAs

Responses	Total votes
Yes	0
No	11
Not yet, maybe in future. It depends on the intended variations and if worksharing will be an advantage for it.	1
Abstention/no entry	2

Evaluation

None of the participants has used worksharing for purely national MAs yet. One participant indicated that it might be an option in the future depending of advantage. Considering the results from question 7, it can be seen that even though worksharing was not used for purely national MAs yet, the participants are aware of this option. Question 7 and 8 were intended to investigate whether worksharing for purely national MAs will have the same level of acceptance and importance as for MRP/DCP. Based on the few responses received, this cannot be evaluated.

9. Do you intend or did you already use Art. 5 procedure(s) since August 4th?
If yes, due to national variations or MRP/DCP?

Table 13: Summary of the responses to question 9 on usage of Article 5 procedures

Responses	Total votes
Yes, variation according §5 on a national basis	1
No	11
Not yet, maybe in future.	1
Abstention/no entry (“No information”)	1

Evaluation

Only one participant has used the Article 5 procedure already, in one answer the “no” was explained by “since the procedure is too time-consuming”. One further answer indicates that the Article 5 procedure might be considered in future. From this it can be concluded, that the participants are aware of this option. Usually, instead of starting an Article 5 procedure directly, first a request is made to the competent authority as this will provide a quick response and solution. This may account for the little number of requests. Another simple explanation is the completion of the catalogue of change categories in the updated Classification Guideline that has been confirmed in question 2 already.

10. Did the BfArM ask for submission of national variations (e.g. for changes in indication, registered pack sizes) for a German MA within a MRP/DCP procedures?

Table 14: Summary of the responses to question 10 on national variations for German MAs within a MRP/DCP procedure

Responses	Total votes

Yes	3
No	3
Not applicable or no entry	8

The answers “Not applicable” (5), “No MRP/DCP in my company” (1) and “Not until Sept 2013 – can’t tell what happened later” (1) as well as no entry were summarised under “Not applicable”. One answer was more specific: “Yes, for ‘Klinikpackungen’ with the same size as the approved package size”.

Evaluation

This question was triggered because the submission of a national variation was demanded by the BfArM for a new pack size for the German market already mentioned in the harmonised SmPC (please refer to: 2.3.1 National variation for a German MA within an MRP/DCP). The intention was to investigate whether this request was an exception. Three participants responded to the question with “yes”. Consequently a request was made to the BfArM in January 2014 for clarification. The response points out that this change is just the inclusion of a pack size that has already been registered in the harmonised SmPC in the national German texts and not a change in pack size. Hence it has to be notified nationally using a notification of change for a change in texts according to section 29(1) AMG (Annex 3: Request to BfArM on national variations for a German MA within a MRP/DCP procedure). This statement is not in line with the practice of the BfArM as experienced from August to December 2013 and as documented in the BfArM’s current list of change items (version 1.8 as per 08.11.2013).[50]

11. Do you have cases, where the agency did not immediately reject an IA variation due to missing documents but allowed to provide the missing documents during validation? If yes, which agencies were concerned and what kind of documents?

Table 15: Summary of the responses to question 11 on amendments of IA variations

Responses	Total votes
Yes, INFRAMED	1
No	10

[50] BfArM’s list of change items, version 1.8 as per 08.11.2013, http://www.bfarm.de/SharedDocs/Formulare/DE/Arzneimittel/Zulassung/aender/Katalogder%C3%84nderungstatbest%C3%A4ndeV18.pdf?__blob=publicationFile&v=3 (25.01.2014 archived by WebCite® at http://www.webcitation.org/6MtGhWuof).

Not applicable or no entry 3

Evaluation

The revised wording in the new, updated Classification Guideline allows the competent authorities to accept amendments of IA variations and prevent resubmissions (please refer to: 2.1.1 Request of further information for IA variations). The intention of question 11 was to investigate whether the authorities use this possibility. Only one participant confirmed the use of this possibility by the Portuguese authority.

2.4.2 Differences updated Classification Guideline versus former national German variation system

12. Please give your agreement/disagreement with below statements. Tick “5” for “I fully agree”, “4” for “I partially agree”, “3” for “undecided”, “2” for “I mostly disagree” and “1” for “I do not agree”:

For this type of tick off questions (question 12, 13, 15, 16, 17, 20 and 21), an average level of agreement (average rate) was determined based on the summation of the individual levels of agreement (1 to 5) and the number of participants. Abstentions were excluded from this calculation. Consequently, an average rate of 3.0 is the arithmetic mean that indicates no trend.

Table 16: Level of agreement on the statements of question 12 on options for grouping

Statements	Average rate
The options for grouping were better in the former national German system compared to the Variations Regulation	3.14
The options for worksharing are better in the Variations Regulation compared to former German national System	3.71
It is good to have the option of submission of worksharing for purely national MAs	3.93

Evaluation

On average, participants seem to be undecided (rate 3.14) whether grouping was better in the former national German system or not. As a matter of fact, 4 participants ticked 1 and 6 ticked 5 whereas 2 each ticked 2 and 3 as level of agreement. Hence, there are two completely

different positions that might depend on the level of experience with the former national German system.

In terms of worksharing there is a clear trend (rate deviates more than 0.5 from 3.0) that the options are better in the Variations Regulation and a general agreement that it is good to have the option of submission of worksharing for purely national MAs.

13. Please tick the boxes as appropriate:

Table 17: Level of agreement on the statements of question 13 on adaption to QRD-Template

Statements	Average rate
Complete adaptation to QRD-Template will now trigger an IB variation for purely national MAs, in case no other IB variation for texts is upcoming.	
Despite the costs, we will submit a complete adaption to QRD-Template in a separate IB variation	3.00
We will include the standard sentence for side effects only to save costs	3.00

Evaluation

The intention of this question was to get an impression of the cost sensitivity of the participants, as complete adaption to the QRD-Template is an option but not a must. Interestingly, the average rate is 3.0 (undecided) and the various levels of agreement of the single participants were distributed rather evenly. This can be interpreted in the following way: The participants want to maintain a high quality in the texts but they weigh up costs and benefits carefully.

14. With Variations Regulation becoming effective for purely national MAs, some useful change items were abandoned, e.g.

    SKNR 1883 Results of stability testing of finished product without change in shelf life

    SKNR 4248 Adaption of texts to QRD-Template according to Version 8 Rev. 2011

    SKNR 1211 Fulfilment of conditions [Auflagenerfüllung]

    What other change items that do not have an equivalent/counterpart in the Classification Guideline do you miss?

    (Please compare with old former German national system, valid until October 2012.)

Table 18: Summary of the responses to question 14 on abandoned SKNR's

Responses	Total votes
No entry	4
Not applicable	4
No experiences	1
None	1
1763 Editorial change	1
We definitely miss an adequate system to correct smaller issues to the texts (PIL/SmPC) in case of faults or mistakes without having a Type IB variation.	2
I miss the listed ones too (1882, 4248, 1211)	1
0204 Information and documents about analytical testing	1

Evaluation

Only four participants contributed to this question. Three of them miss SKNR 1763, or in words, the possibility to correct smaller issues in the texts independently from a type IB variation. An appropriate variation IA is lacking in the Classification Guideline.

For adaption to QRD-Template and fulfilment of sanctions workarounds are available, but in terms of "Results of stability testing of finished product without change in shelf life" there will be a variation IB (unforseen) required. As a consequence such data might not be submitted anymore in order to save costs.

IA variations should be possible for small corrections in the texts and for submission of results of stability testing that do not change shelf life or storage conditions.

SKNR 0204 "Information and documents about analytical testing" was formerly used to submit minor and major changes in analytical procedures as a simple "tell and do" notification of change. It is still available in the BfArM's current list of change items (version 1.8 as per 08.11.2013) [51], but of course not available for purely national MAs under the scope of the Variations Regulation anymore.

Only SKNR 1211 "Fulfilment of conditions [Auflagenerfüllung]" really vanished from the list of change items and is not even available for the purely national MAs outside of the scope of the Variations Regulation. However, only one participant had missed it.

[51] BfArM's list of change items, version 1.8 as per 08.11.2013, http://www.bfarm.de/SharedDocs/Formulare/DE/Arzneimittel/Zulassung/aender/Katalogder%C3%84nderungstatbest%C3%A4ndeV18.pdf?__blob=publicationFile&v=3 (25.01.2014 archived by WebCite® at http://www.webcitation.org/6MtGhWuof).

15. Please give your agreement/disagreement with below statements. Tick “5” for “I fully agree”, “4” for “I partially agree”, “3” for “undecided”, “2” for “I mostly disagree” and “1” for “I do not agree”.

Table 19: Level of agreement on the statements of question 15 (implications of the inclusion of German purely national MAs in the scope of the Variations Regulation)

Statements	Average rate
Due to the inclusion of German purely national MAs in the scope of the Variations Regulation…	
we save time	2.50
the workload decreased	2.50
we have to employ more people	2.42
we will save costs	2.50
the number of submissions increased	3.31
variation tracking became easier	3.38
the submission process is faster compared to former national German System	2.46
we will withdraw German purely national MAs due to increased amount of work for maintenance	1.83
we will withdraw German purely national MAs due to increased costs for maintenance	1.83
we might have SCM issues/out of stock problems due to loss of former national tell-and-do variations	2.20
it is difficult to submit an update of the dossier to current state of scientific and technical progress (e.g. inclusion of process validation protocols, stability data)	3.29
it is more expensive to accomplish an update of the dossier to current state of scientific and technical progress (e.g. inclusion of process validation protocols, stability data)	3.36

Evaluation

There is a clear trend (rate of 2.50) indicating that workload and costs increased and no time is saved due to inclusion of the German purely national MAs in the scope of the Variations Regulation. In line with this observation, the number of submissions slightly increased (average rate 3.31) and the submission process is not faster than in the former national German System (average rate 2.46).

Moreover, German purely national MAs will not be withdrawn due to increased amount of work (average rate 1.83) or increased costs (average rate 1.83).
The risk of SCM issues or even out of stock problems due to loss of former national "tell and do" variations is considered low (average rate 2.20).
Solely variation tracking became slightly easier (average rate 3.38).

It is slightly more difficult (average rate 3.29) and expensive (average rate 3.36) to submit and accomplish an update of the dossier to current state of scientific and technical progress.

On the other hand, the level of agreement is only 2.42 when asked whether more people have to be employed. Apparently the additional work has to be accomplished without additional costs for staff.

2.4.3 Management of the transition

16. Please give your agreement/disagreement with below statements. Tick "5" for "I fully agree", "4" for "I partially agree", "3" for "undecided", "2" for "I mostly disagree" and "1" for "I do not agree":

Table 20: Level of agreement on the statements of question 16 on usage of CESP

Statements	Average rate
We have already started to work with the CESP-System (Common European Submission Platform) …	
to save time	4.36
to save costs	4.55
to speed up the submission process	4.00
to upload more files than possible in PharmNet.Bund	4.20
due to other reasons such as (please state)[52]	1.67

[52] No other reasons were stated in the last question.

Evaluation

After inclusion of the purely national MAs in the scope of the Variations Regulation, the PharmNet.Bund portal for submissions was changed immediately. Along with this adaption, the number of separate files that can be uploaded together with one variation was reduced.
This shortcoming could be overcome by using CESP in addition to the PharmNet.Bund portal. Question 16 intended to investigate whether the participants have already used this short-term solution.

Eleven of fourteen participants (3 abstentions) of the survey agreed, that they already started to use CESP. When asked for the reasons, the statement “to save costs” reached the highest level of agreement (4.55). Clear agreement (more than 4.0) was also given to the statements “to save time”, “speed up submission” and “to upload more files than possible in PharmNet.Bund” (also refer to question 19).

Hence, the findings from question 15 that no saving of time or costs or decrease in workload was achieved due to the inclusion of the purely national MAs in the scope of the Variations Regulation, cannot be seen as a temporary phenomenon that will vanish soon. The advantages of CESP are already used but no overall saving of time and costs has been observed yet.

17. Please tick the boxes as appropriate:

Table 21: Responses to question 17 (number of MAs not under the scope of the Variations Regulation)

Statements	more than 20	less than 20	less than 10	less than 5	no	no entry
We still have German purely national MAs that are not under the scope of the Variations Regulation:						
homeopathic medicinal products and traditional herbal medicinal products	1		2		9	2
Marketing authorisations for Parallel import	1			1	9	3
standardised marketing authorisations ("Standardzulassung")	1	1		3	6	3
others: (Please give details)	1				3	10

Evaluation

This question was included in order to allow to investigate whether the number of German purely national MAs that are still not under the scope of the Variations Regulation is related to positive or negative ratings on the statements of question 15, line 1, 2 and 4 (we save time, the workload decreased, we will save costs). Only two participants had more than 20 of such MAs, one of them had less than 10 homeopathic and traditional herbal medicinal products but more than 20 MAs each for parallel import and standardised marketing authorisations. No comments were received on the last question "others: (Please give details)".

For each participant, a correlation was made with his respective responses to question 15:

Table 22: Correlation of workload and costs with the number of German purely national MAs that are not under the scope of the Variations Regulation (combined data from question 15 and 17)

Number of German purely national MAs that are not under the scope of the Variations Regulation (Number of participants)	more than 20 (2)	less than 20 (1)	less than 10 (1)	less than 5 (3)	none or not known (5+2)
we save time	4	2	2	2	2.4
the workload decreased	3.5	4	1	2	2.4
we will save costs	3.5	3	1	2.7	2.3
Average rate	3.67	3.00	1.33	2.22	2.38

Figure 2: Correlation of workload and costs with the number of German purely national MAs that are not under the scope of the Variations Regulation (combined data from question 15 and 17).

The assumption that the more MAs are still outside of the scope of the Variations Regulation the less benefit of the harmonisation of purely national MAs with the Variations Regulation will be observed was not confirmed. With an average level of agreement of 3.67, time and costs are saved slightly when more than 20 MAs are still outside of the scope of the Variations Regulation.
Checking back with one participant, that had more than 20 of such MAs and fully agreed to save time and costs, revealed that homeopathic medicinal products and traditional herbal medicinal products are often handled by different departments than the chemical active ingredients.
This seems to be not the case in companies having less than 10 medicinal products left outside of the Variations Regulation. With a clear average rate below 2.50, this group has to spend more time and money due to handling of the two systems in parallel in one department.

Even the participants that have no MAs left outside of the scope of the Variations Regulation to handle (this group includes two consultants) clearly disagree with statements of saving time or costs.

18. Do you have any paradox situations in your dossiers for purely national MAs, that cannot be solved with the Classification Guideline? (E.g. a manufacturing site was notified in former German national system but no further work was done as required by classification guideline - how to submit missing documentation like process validation scheme or report?)

Table 23: Level of agreement on the statements of question 18 - paradox situations

Response	Total votes
No	5
Not applicable or no entry	4
Yes, to be solved with IB-variations.	1
Yes, we have those situations especially when it comes to manufacturers.	1
Yes, for example: Submission of stability data without extension of shelf life. There is no possibility for a submission of follow-up stability data after completion of stability studies based on the post-approval stability commitment.	1
Main problem is correction of errors in the dossier and dossier update. Switch from NtA format to CTD requires many variations that are not classified. ASMF update requires many variations that are not classified if you want to avoid a type II variation.	1
IB z) variations solve all problems	1

Evaluation

Five participants answered “no” and four entered “not applicable” or made no entry. So the problem is only apparent to less than half of the participants.

Two participants admit that there are problems and that they can be solved by means of unforeseen IB variations.

Three participants give specific examples. Once again, submission of stability data without change in shelf life is mentioned.

The presence of paradox situations is confirmed especially when it comes to manufacturers.

Likewise, problems occur in connection with correction of errors in the dossier. The switch from the old dossier format (NTA, Vol. 2B; edition 1998) to current the dossier format “EU-CTD” (NTA, Vol. 2B, edition May 2006) seems to be a challenge and expensive as it triggers unforeseen IB variations.

Eventually, when avoiding a type II variation, an ASMF update becomes a challenge as well.

19. Is the current PharmNet.Bund adaption for submission of national Variations sufficient or which improvements are desired?

Table 24: Summary of the responses to question 19 on curent PharmNet.Bund

Response	Total votes
Yes/sufficient	4
No experiences or no entry	7
More space for more files (attachments) needed	3

One participant stated “Sufficient in combination with CESP”, the response was rated under “More space for more files (attachments) needed”.

Evaluation

As already mentioned in question 16 (CESP), the number of separate files that could be uploaded together with one variation has been reduced since 04.08.2013 in the PharmNet.Bund portal. This limits the use of the portal in practice and makes it necessary to use workarounds.

One possibility is to use CESP in combination with the PharmNet.Bund portal. The other workaround is combination of several different PDF-attachments like highlighted SmPC(s) and PL(s) in one PDF. Both workarounds require additional time and effort. One response obtained pinpoints this problem nicely:

> “No, it is a disadvantage that only few files can be uploaded as attachments. Therefore an additional submission via CESP and time for its submission are necessary.”

2.4.4 Differences between variations to MRP/DCP and purely national MAs

20. Please give your agreement/disagreement with below statements. Tick "5" for "I fully agree", "4" for "I partially agree", "3" for "undecided", "2" for "I mostly disagree" and "1" for "I do not agree":

Table 25: Level of agreement on the statements of question 20 on grouping and observance of deadlines

Statements	Average rate
For submission and tracking of variations and national variations we follow the very same process.	3.54
In spite of the fact that the national variations are now under the scope of the Variations Regulation, we feel that it is like a second national system due to the adaptions and national peculiarities like creation of procedure number and different importance of status mails.	2.85
The options for grouping at BfArM are better for German purely national MAs than for MRP/DCP procedures	3.00
In my experience, purely national variations are processed more slowly than MRP/DCP submissions.	3.00
In my experience, variations to MRP/DCP procedures with RMS DE and no CMS are processed more slowly than MRP/DCP procedures with CMS.	2.82
BfArM conforms to the deadlines for variations to MRP/DCP procedures with RMS DE and no CMS	3.17
BfArM conforms to the deadlines for variations to MRP/DCP procedures with RMS DE and one or more CMS	3.50
Validation and assessment of national variations at BfArM is according to the deadlines	3.46
Validation and assessment of MRP/DCP variations at BfArM is according to the deadlines	3.50
When grouping exclusively IA variations of a MRP/DCP procedure, did you experience restrictions to categories made by the RMS?	2.67
When grouping exclusively IA variations of a purely national MAs did you experience restrictions to categories made by BfArM?	2.42

Evaluation

The average level of agreement to the first questions indicates a trend (3.54), that variations and national variations are handled by the same process. But the individual responses are not distributed evenly: 4 participants did not agree, one was undecided and 8 agreed. In addition there was one abstention.

The second question may serve as a control of the first question. But there is no clear trend (rate 2.85) that the national variations are not seen as a second national system. The individual responses are distributed more evenly in this case: 5 disagreed, 4 were undecided and 4 agreed. In addition there was one abstention.

Even though the BfArM allows generous grouping of change items in national variations[53] (also refer section 2.2.5 Adaptions of BfArM for purely national MA due to the switch to the Variations Regulation), surprisingly the responses show no trend (3.0) in favour of this.

Asked whether national variations or variations to MRP/DCP procedures with RMS DE and no CMS are processed more slowly than MRP/DCP procedures with CMS, the participants are undecided (rate 3.00 and 2.82 respectively). No trend can be determined and the single responses are distributed evenly. The lack of a clear disagreement has to be noted.

The participants are undecided on the question whether the BfArM conforms to the deadlines for variations to MRP/DCP procedures with RMS DE and no CMS (rate 3.17). In the presence of CMS, the participants slightly agree that BfArM conforms to the deadlines for variations (rate 3.50). Based on this small difference between the level of agreement, it is not possible to state whether procedures with CMS are treated on higher priority or not.
This is in line with the answers to the previous two questions on different treatment of national variations and variations without CMS.

In terms of validation and assessment within the deadlines, here is no difference between national variations (3.46) and variations (3.50) at BfArM. The lack of a clear agreement like for example a rate over 4.0, indicates that deadlines are not always met.

The two questions on restrictions to categories made by the competent authority when grouping exclusively IA variations aimed to investigate further the experience from first submissions in September 2013 that indicated that the combination of changes of chapters B and C of the Classification Guideline was restricted even in case of grouping solely IA variations (refer to section 2.2.5, paragraph on generous grouping).

[53] Bekanntmachung über die Anzeige von Variations für rein nationale Zulassungen gemäß Kapitel IIa der Verordnung (EG) Nr. 1234/2008 ab dem 04.08.2013, die gemäß § 77 AMG in die Zuständigkeit des BfArM fallen vom 12. Juli 2013, http://www.bfarm.de/SharedDocs/Bekanntmachungen/DE/Arzneimittel/aender/bm-aender-20130712-Anzeige.pdf?__blob=publicationFile&v=4
(19.01.2014; archived by WebCite® at http://www.webcitation.org/6Mk7Xo8Gj).

With a rate of 2.67 only a slight disagreement is observed in case of the MRP/DCP procedures, whereas the rate of 2.42 for national variations shows a trend that grouping is not restricted to categories by BfArM. This result is in line with confirmation obtained from BfArM in January 2014, that there are no restrictions to certain chapters for grouped applications that contain only IA variations (Annex 2: Request to BfArM on grouping of IA variations).

21. Please give your agreement/disagreement with below statements. Tick "5" for "I fully agree", "4" for "I partially agree", "3" for "undecided", "2" for "I mostly disagree" and "1" for "I do not agree":

Table 26: Level of agreement on the statements of question 21 on implicit approval

Statements	Average rate
Implicit approval of IB variations works well for …	
purely national MAs at BfArM	3.36
MRP/DCP submissions at BfArM as RMS	3.60
MRP/DCP submissions at other RMS	3.36

Evaluation

By contrast to question 6 on confidence in implicit approval in general, the purpose of this question was to identify different levels of confidence depending on MA and competent authority. Again, the participants are mainly undecided on whether implicit approval of IB variations works well or not. Considering the individual responses, most participants ticked undecided. The range of abstentions is 3-4. With BfArM as RMS, there is a trend (rate 3.6) indicating that implicit approval works.

This result correlates with the results from question 6 on implicit approval, were 5 participants used the implicit approval whereas 5 participants did not or only with limitations. The number of abstentions was 4.

Hence, there is still an uncertainty connected with the implicit approval after 30 days. With BfArM as RMS, there is less uncertainty compared to other RMS. In case of national variations, the confidence in BfArM is slightly smaller and on the same level as other RMS (rate 3.36).

22. Did you experience any partial approvals of IA-variations for MRP/DCP procedures since 01/2010 (e.g. only a part of the submitted change in SmPC was approved)? If yes, who was the agency acting as RMS and did partial approvals save time or spare resubmission?

Table 27: Summary of the responses to question 22 on partial approvals of IA variations

Response	Total votes
Yes (RMS DE)	1
No	9
Not applicable or no entry	4

Evaluation

Only one participant experienced a partial approval so far within an MRP with three additional CMS and no resubmission was required.

23. Did you experience any partial approvals of IA-variations for purely national MAs since 08/2013? If yes, did partial approvals save time or spare resubmission?

Table 28: Summary of the responses to question 23 on partial approvals of IA national variations

Response	Total votes
Yes, due to lack of experience in how to use the Variations Regulation for national variations in the beginning	1
Yes, editorial changes in texts submitted along with IA were not accepted; resubmission along with next IB.	1
No	8
Not applicable	2
Abstention/no entry	2

Evaluation

Only two participants experienced a partial approval so far for national variations IA. This number seems too low. As partial approvals are better than complete rejections their increased use could save a lot of time and work.

24. Are there any points, where the BfArM treats purely national MAs different than variations in MRP/DCP/CP?

Table 29: Summary of the responses to question 24 on different treatment of variations

Response	Total votes
In terms of purely national MA the BfArM seems to be more complaisantly; processing seems to be faster and grouping is handled more generously.	1
No	3
Not applicable or no experience	7
Abstention/no entry	2
Nevermind! Before the implementation of the updated Classifiaction Guideline in Germany the variation system was easy to handle, proved high efficacy, and needed less bureaucracy. BfArM's principle based on the legal self-responsibility of the MAH and defined list of major variations. The rest were just barely notifications. That meant that the approval of approval procedures had to be expected after 3 months. Then the advantage for Germany was to achieving a EU system that is simple as the German national system.	1

Evaluation

Three participants stated that there is no different treatment of variations and national variations. Only two participants described differences.

The statements of the first answer are in accordance with the communication of the BfArM that defines generous rules for grouping and affirms to respect the validation deadlines.[54]

The last answer is more a general statement on the advantages of the former national German variation system.

[54] Bekanntmachung über die Anzeige von Variations für rein nationale Zulassungen gemäß Kapitel IIa der Verordnung (EG) Nr. 1234/2008 ab dem 04.08.2013, die gemäß § 77 AMG in die Zuständigkeit des BfArM fallen vom 12. Juli 2013, http://www.bfarm.de/SharedDocs/Bekanntmachungen/DE/Arzneimittel/aender/bm-aender-20130712-Anzeige.pdf?__blob=publicationFile&v=4
(19.01.2014; archived by WebCite® at http://www.webcitation.org/6Mk7Xo8Gj).

3 Discussion

Effective since 04.08.2013 the German purely national marketing authorisations have been included in the scope of the Variations Regulation and the new, updated Classification Guideline of 2013 has come in force as well. The consequences of this inclusion and the changes in the updated Classification Guideline were investigated. In order to assess the practical implications a survey was conducted and evaluated.

3.1 Differences between former and updated Classification Guideline

The differences between former and updated Classification Guideline are based on updated classification, corrections, additions, adaption to new legislation and the inclusion of nineteen former Article 5 recommendations. Additionally, the Classification Guideline was amended with procedural guidance on the handling of variations.

The amendments made to the descriptions and conditions of changes result in better understanding of their scope and applicability. More clarity is given on special topics like deletion of a non-significant parameter and changes in batch size. Moreover, gaps were closed by addition of new subitems to several different change categories.
Furthermore, there are few downgrades to a lower procedure type. For example, implementation of wording already agreed by the competent authority is now accepted as IAIN (formerly IB) variation on condition that it does not require the submission of additional information and/or further assessment.

According to the results of the survey, the main expectation was completion of the catalogue of change categories, closing of gaps and inclusion of Article 5 recommendations.
When asked for first experiences with the updated Classification Guideline, the answers indicate that the main expectation, completion of the catalogue of change categories, was at least partially met, or as responded in the survey: “some gaps in categorisation are closed but not all of them.” When asked for advantages, the answers show that the updated Classification Guideline has an improved and comprehensive catalogue of change categories and the amendments are appreciated.

In conclusion, the updates make the use of the new, updated Classification Guideline easier and more convenient in practice. Nevertheless, according to the responses obtained in the survey, there seems to be still some room for improvement.

In contrast to the former Classification Guideline of 2010, the Classification Guideline of 2013 also contains procedural guidance on the handling of variations. Thus, information formerly distributed over former Classification Guideline and "CMDh best practice guides for the submission and processing of variations in the mutual recognition procedure" [55] has been combined in the updated Classification Guideline. This is another simplification that facilitates the use in practice.

As described earlier (2.1.1 Request of further information for IA variations), the new, updated Classification Guideline allows the competent authorities to accept amendments of IA variations and prevent resubmissions. Using this option will help to reduce the workload on both, the applicants and the competent authorities' side. At least one participant confirmed the use of this option by the Portuguese authority (evaluation of question 11 of the survey). Based on personal communication[56] the BfArM should be also mentioned among the authorities that use above option in a very supportive way.

Moreover, the procedural guidance in the updated Classification Guideline describes the implicit approval obtained for IB variations within 30 days following the acknowledgement of receipt of a valid notification in detail. The intention might have been to create better awareness and to encourage applicants to rely on the implicit approval more than in the past.
Question 6 of the survey was intended to evaluate the current use of the implicit approval. The responses revealed that there is still an uncertainty connected with the implicit approval after 30 days. This might be based on different experience with the various authorities.

Building confidence in the implicit approval is especially important in case of the German purely national MAs, since there will be no official approval mails sent to the applicant as mentioned earlier (2.2.5 Adaptions of BfArM for purely national MA due to the switch to the

[55] CMDh best practice guides for the submission and processing of variations in the mutual recognition procedure (Doc. Ref.: CMDh/094/2003/Rev.19 of February 2013)
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Variations/CMDh_094_2003_Rev.19_2013_03_Clean.pdf
(28.12.2013; archived by WebCite® at http://www.webcitation.org/6MD1CKwbB).
[56] betapharm Arzneimittel GmbH, regulatory affairs department, personal communication (06.01.2014).

Variations Regulation). Instead the status mails are legally binding. Moreover, the status mails on positive closure might be delayed. For this reason, applicants are strongly advised to carefully track the status mails received on positive validation (status 'in progress'), as they indicate the beginning of the 30 day period.
In order to provide legal certainty to applicants as soon as possible, for IA and IB variations status mails on positive validation and approval, respectively, should be sent automatically after expiry of the regulatory time limit of 30 days.

Under "4. Annex" the updated Classification Guideline contains an opening clause for type II variations. The applicant can submit a type II variation for several minor changes, on grounds of the overall impact of these changes on the quality, safety or efficacy of the medicinal product. This is indeed the reintroduction of the former "Umbrella Type II Variation" that had already been supported strongly in the master thesis of Angelika Kamp from 2012.[57] Interestingly, one participant of the survey typed "Reintroduction of the Umbrella Type II Variation" under question 1 "expectations" but did not mention the new possibility in the following questions 2 and 3 as an advantage. A reason might be that the wording of the opening clause for type II variations in the annex is a bit vague. As the last sentence of the opening clause mentions IB variations as well, it should also be possible to combine several IA variations in one IB variation were reasonable and with reference to the overall impact of these changes.
Proper use of the opening clause will help to save costs and decrease the workload. Hence, the opening clause is one of the major improvements in the updated Classification Guideline.

The handling of editorial changes was amended in the updated Classification Guideline as well. A similar paragraph on editorial changes had already been contained in the former Classification Guideline, but the request to identify the editorial changes in the application form and the definition of editorial changes were missing.
This substantiates further the above findings, that the Classification Guideline has been revised comprehensively and with due care. To support this view, it should be mentioned that the Directorate General Health and Consumers of the European Commission initiated a public

[57] Angelika Kamp, MDRA master thesis, "2 years Variation Regulation: A retrospective critical assessment from the industrial perspective", Bonn, 2012, p. 49, http://dgra.de/media/pdf/studium/masterthesis/master_kamp_a.pdf (15.02.2014; archived by WebCite® at http://www.webcitation.org/6NP1PZ4T8).

consultation on the draft of the updated Classification Guideline in June 2012 and considered the recommendations.[58]

3.2 Implication of the Variations Regulation for national MAs

The former national German variation system was appreciated because it was very convenient, had no limitations for grouping of change items, no validation phase and most change items did not require prior approval.[59] It was considered beneficial, very clear and effective compared with the European variation system.[60] Consequently, the inclusion of the German purely national marketing authorisations in the scope of the Variations Regulation was expected to "…immensely increase workload and costs as well as prolong the timelines of regulatory submissions" which "…will require additional man power and increased budgets for the Regulatory Affairs Departments".[61] The above statements and assumptions were examined in the survey and one response gets to the heart of this:

> "…Before the implementation of the updated Classification Guideline in Germany the variation system was easy to handle, proved high efficacy, and needed less bureaucracy. BfArM's principle based on the legal self-responsibility of the MAH and defined list of major variations. The rest were just barely notifications. That meant that the approval of approval procedures had to be expected after 3 months. …".

A similar response was also received as accompanying text of a returned questionnaire.

Yet, the results of the survey suggest that for companies holding several purely national MAs for the very same medicinal product in different member states, the inclusion of the purely national MAs in the scope of Variations Regulation results in saving time and money, easier variation tracking and reduced workload.

In the other scenario, where a company maintains many purely national MAs for different medicinal products in Germany, the benefits of harmonisation do not take effect. In this case

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[58] Directorate General Health and Consumers of the European Commission, http://ec.europa.eu/health/better-regulation-variations-regulations-developments_en.htm, (09.02.2014; archived by WebCite® at http://www.webcitation.org/6NFvhQQBr).

[59] For more details please refer to: Dr. Verena Tautorat, DGRA master thesis, "The end of an era: Implementing Variation Directive 2009/53/EC into German Drug Law", Bonn, 2011, page 38 et seq. http://dgra.de/media/pdf/studium/masterthesis/master_tautorat_v.pdf (15.02.2014; archived by WebCite® at http://www.webcitation.org/6NP0iItiR).

[60] BPI comments to public consultation "Review of Commission Regulation (EC) No. 1234/2008" from 18/10/2011, http://ec.europa.eu/health/files/betterreg/pc_result_pn_2011/18_pc_result_pn_2011.pdf (02.02.2014; archived by WebCite® at http://www.webcitation.org/6N5VPI8ti).

[61] Angelika Kamp, MDRA master thesis, "2 years Variation Regulation: A retrospective critical assessment from the industrial perspective", Bonn, 2012, p. 53, http://dgra.de/media/pdf/studium/masterthesis/master_kamp_a.pdf (15.02.2014; archived by WebCite® at http://www.webcitation.org/6NP1PZ4T8).

it is quite the opposite: the maintenance of purely national MAs has become more expensive, time consuming and complex.
Overall, according to the responses to question 15 of the survey, workload and costs increased and no time is saved by the MAH due to inclusion of the German purely national MAs in the scope of the Variations Regulation. In addition to this, the submission process is not faster than in the former national German system.

Contrasting above findings, according to the survey German purely national MAs will not be withdrawn due to increased amount of work or increased costs. Neither additional staff will be recruited. Apparently the additional work has to be accomplished without additional personnel costs.

The assumption that the more MAs are still outside of the scope of the Variations Regulation the less benefit of the harmonisation of purely national MAs with the Variations Regulation will be observed was not confirmed (see evaluation of questions 15 and 17).
One interpretation of this finding is that, in case of many MAs outside of the scope of the Variations Regulation, they are handled by different departments than the MAs within the scope of the Variations Regulation. This seems to be not the case in companies having less than 10 medicinal products left outside of the scope of the Variations Regulation. Consequently, these companies have to spend more time and money due to handling of the two systems in parallel in one department.

On the question whether grouping was better in the former national German system or not, there are once more two completely different positions that might depend on the level of experience with the former national German system. Whereas one part of the participants appreciates the possibilities of the unlimited grouping of the former national German system, this possibilities may confuse the other part of the participants that might prefer more guidance.
The new option of using worksharing procedures for purely national MAs as well, was appreciated in the survey. However, none of the participants has used worksharing for purely national MAs yet. Based on the few responses received, the question whether worksharing for purely national MAs will have the same level of acceptance and importance as for MRP/DCP could not be evaluated.

According to the responses to question 15 of the survey, it is deemed slightly more difficult and expensive to submit and accomplish an update of the dossier to current state of scientific and technical progress in the European variation system. This statement is supported by the answers given to question 14: Despite the improved and comprehensive catalogue of variation categories, the possibility to correct smaller issues in the texts independently from a type IB variation is missing in the updated Classification Guideline. The same applies for updating of data in the dossier such as submission of results of stability testing of the finished product without change in shelf life or storage condition.

As a consequence such corrections and data might not be submitted anymore in order to save costs. Although the participants want to maintain a high quality in the texts (see evaluation of question 13), they weigh up costs and benefits carefully.

To encourage the submission of such updates of the dossier, IA variations should be possible for small corrections in the texts as well as the submission of data that do not trigger any further amendments. But this is contrary to the view that wherever any assessment is deemed necessary, at least a variation IB has to be submitted.

An alternative, purely national solution could be a prudent revision of AMG Fees Ordinance (AMGKostV). Reduced fees, in the range of the fees of IA variations, could be set for IB variations that require only very little assessment.

3.3 Transition phase and special cases

The transition phase was surely a challenge for both, MAH and competent authorities. It was accompanied by transient phenomena and special cases, as discussed in the following.

PharmNet.Bund

Right after inclusion of the purely national MAs in the scope of the Variations Regulation, the BfArM had to make the necessary adaptions in the PharmNet.Bund portal for submissions. It mastered this challenge rapidly, but since then the number of separate files that could be uploaded together with one variation had been reduced in PharmNet.Bund. This limits the use of the portal in practice and makes it necessary to use workarounds. One possibility is the combination of several different PDF-attachments one PDF to reduce the number of files.

Another possibility to compensate for this disadvantage is using the CESP-System in combination with PharmNet.Bund for submission. File size and amount of files are not limited in CESP.

Indeed, most participants of the survey already started using CESP to save time, costs, speed up submission and have a workaround for the PharmNet.Bund portal's limitation in uploads. However, no overall saving of time and costs has been observed since the inclusion of the purely national MAs in the scope of the Variations Regulation. Hence, this observation cannot be seen as a transient phenomenon of the changeover that will vanish soon.
Allowing simply more uploads in the PharmNet.Bund portal would save the applicants plenty of time and costs.

Paradox situations

The participants of the survey confirmed, that paradox situations arise for purely national MAs during transition that cannot be solved with the Classification Guideline. The presence of paradox situations was confirmed especially when it comes to manufacturers. Once again, submission of stability data without change in shelf life was mentioned. In case a renewal is still necessary, submission of stability data in the course of a renewal application might be an option.
Likewise, transition problems occur in connection with correction of errors in the dossier. The switch from the old dossier format (NTA, Vol. 2B; edition 1998) to the current dossier format "EU-CTD" (NTA, Vol. 2B, edition May 2006) seems to be a challenge and expensive as it triggers unforeseen IB variations. As there are still many MAs based on dossiers in the old format or a mixed format, a simple pragmatic solution is needed. One solution would be the acceptance of conversion to EU-CTD format along with any type II or IB variation that affects Module 3 (former Part II) of the dossier.

Generous grouping of national variations

First experience of September 2013 indicated that the combination of not related variations of chapters B and C of the Classification Guideline was not accepted by the BfArM in case of grouping solely IA variations. In January 2014 the BfArM clarified on request that this restriction only applies if IB or type II variations are included in the grouped application. (Annex 2: Request to BfArM on grouping of IA variations). The results of the survey confirm that the experiences of September 2013 were only exceptional cases. Meanwhile a corresponding entry is available on the BfArM homepage.[62] In summary, grouping of German national variations is remarkably facilitated compared to variations to MRP/DCP.

[62] http://www.bfarm.de/SharedDocs/FAQs/DE/Arzneimittel/aender/variareg/D_grouping/D_varia-ca.html?nn=4287354 (06.02.2014; archived by WebCite® at: http://www.webcitation.org/6NBvw5nCV).

Adaption of the fees

Another part of the transition is the adaption of the fees. The lower costs of notifications of change versus the respective MRP/DCP variation fees have been considered as one of the advantages of the former national German variation system. The inclusion of the purely national MAs in the scope of the Variations Regulation was expected to increase workload and costs dramatically, especially if the current variation fees were just applied for the national variations as well.[63]

In January 2014 a first non-public draft of the AMGKostV of the BMG dated 30.01.2014 was circulated.[64] In terms of national variations the proposed fees are in the range of the previous fees for notifications of change according to Section 29 AMG. Moreover, the proposed fee rates range between the German RMS- and CMS-fees for variations, but are closer to the lower CMS-fees. As the fees for national variations are still provisional, this reasonable approach has to be considered when discussing the costs.

Interestingly, the non-public draft proposes reduced fees for very basic IA variations such as a change in name of the MAH. This favourable approach should be extended to IB variations that require very little assessment as suggested earlier in this discussion.

Moreover, for MRP/DCP having Germany as RMS but no more CMS, the same fees should be charged as for purely national MAs due to similar processing efforts.

National variations for a German MA within a MRP/DCP

As confirmed in the survey, the BfArM demanded submission of a national variation for a German MA within a MRP/DCP. The examples include notification of a new pack size for the German market already mentioned in the harmonised SmPC.

Based on this example, a request was made to the BfArM in January 2014 for clarification. The response points out that such a change is just the inclusion of a pack size that has already been registered in the harmonised SmPC, in the national German texts and not a change in pack size. Hence, it has to be notified nationally using a notification of change for a change in texts according to section 29(1) AMG (Annex 3: Request to BfArM on national variations for a German MA within a MRP/DCP procedure). This position is very transparent and

[63] Angelika Kamp, MDRA master thesis, "2 years Variation Regulation: A retrospective critical assessment from the industrial perspective", Bonn, 2012, page 53, http://dgra.de/media/pdf/studium/masterthesis/master_kamp_a.pdf (15.02.2014; archived by WebCite® at http://www.webcitation.org/6NP1PZ4T8).

[64] BMG, AMGKostV, non-public draft of 30.01.2014, personal e-mail communication of Bundesverband der Arzneimittel-Hersteller e.V., (31.01.2014).

comprehensible. Meanwhile, a statement supporting this view is available in the FAQ-section on the BfArM homepage.[65]

Unfortunately, the current practice of the BfArM does not follow this position as confirmed by the participants of the survey and as documented in BfArM's current list of change items (version 1.8 as per 08.11.2013).[66] Under SKNR 0102 (pack size) of this list details for the national notification of already approved pack sizes in MRP/DCP are given. According to the list, the change item SKNR 0102 (pack size) requires prior approval which is pointless in case of already approved pack sizes in MRP/DCP.

In summary, for inclusion of an already approved pack size in the German texts of a German MA within a MRP/DCP, three different approaches are being followed by the BfArM currently:

- a national variation of the category B.II.e.5
- a notification of change using SKNR 0102 (pack size)
- a notification of change to change the national German texts

This indicates that the internal coordination at BfArM is still ongoing. Indeed, on further request made to the BfArM in February 2014 in this matter, it was confirmed that the request initiated anew an internal coordination process.[67]

Non-variations - Changes in the non-official part of the labelling

Changes in labelling or PL outside of the SmPC can be submitted via the procedure defined in Article 61(3) of Directive 2001/83/EC in case of MRP/DCP. For purely national MAs where no harmonised position is to be maintained, the changes in labelling or PL outside of the SmPC should be submitted by means of a national notification of change according to Section 29(1) AMG. As Directive 2001/83/EC has been transposed into the German AMG, this approach is justified for purely national MAs.

Nevertheless, in November 2013 a change in the non-official part of the labelling (additional brief description for opening of blister) had to be submitted as a non-variation according to

[65] http://www.bfarm.de/SharedDocs/FAQs/DE/Arzneimittel/packungsgroessen/aa_FAQ03.html?nn=3863448 (15.02.2014; archived by WebCite® at http://www.webcitation.org/6NP9OceHQ).
[66] BfArM's list of change items, version 1.8 as per 08.11.2013, http://www.bfarm.de/SharedDocs/Formulare/DE/Arzneimittel/Zulassung/aender/Katalogder%C3%84nderungstatbest%C3%A4ndeV18.pdf?__blob=publicationFile&v=3 (25.01.2014 archived by WebCite® at http://www.webcitation.org/6MtGhWuof).
[67] BfArM, Division licensing, Simplified procedures II, personal e-mail communication (19.02.2014).

Article 61(3) of Directive 2001/83/EC for a purely national MA.[68] The notification form had to be modified accordingly as it was not intended for purely national MAs.
This gives rise to the question, whether an Article 61(3) procedure can legally change directly a German purely national MA. Moreover, it remains unclear how the obligation to submit a national notification of change according to Section 29(1) AMG was suspended.
Upon request to the BfArM in February 2014 it was indicated that the topic is internally still under discussion.[69]

3.4 Differences between variations to MRP/DCP and purely national MAs

German national variations do have peculiarities like creation of procedure number and different importance of status mails. The question in the survey whether the national variations are seen as a second national variation system did not provide a trend neither in favour nor against. At least there was a trend observed, that applicants handle variations and national variations by the same process.

As described above, grouping of German national variations is remarkably facilitated compared to variations. The BfArM allows in general generous grouping of variations to purely national MAs.[70] Surprisingly the responses on the respective question in the survey showed no trend. One reason might be that the awareness of these possibilities is too low.

In contrast to MRP/DCP, no other member states are involved in variations to purely national MAs. This gave rise to the question, whether the authorities might handle national variations differently, for example in terms of priority and complaisance.
On the question whether national variations or variations to MRP/DCP procedures with RMS Germany and no CMS are processed more slowly than MRP/DCP procedures with CMS, the survey revealed no trend. In fact, most participants ticked “undecided”.
The results indicate that deadlines are not always met, but there is no indication that national variations are disadvantaged. This interpretation is supported by the results of the questions

[68] betapharm Arzneimittel GmbH, regulatory affairs department, submission of 21.11.2013, personal communication (14.01.2014).
[69] BfArM, Division licensing, Simplified procedures II, personal communication (14.02.2014).
[70] Bekanntmachung über die Anzeige von Variations für rein nationale Zulassungen gemäß Kapitel IIa der Verordnung (EG) Nr. 1234/2008 ab dem 04.08.2013, die gemäß § 77 AMG in die Zuständigkeit des BfArM fallen vom 12. Juli 2013, http://www.bfarm.de/SharedDocs/Bekanntmachungen/DE/Arzneimittel/aender/bm-aender-20130712-Anzeige.pdf?__blob=publicationFile&v=4
(19.01.2014; archived by WebCite® at http://www.webcitation.org/6Mk7Xo8Gj).

whether validation and assessment of variations respectively national variations are according to the deadlines at BfArM. Almost the same level of agreement - between “undecided” and “I mostly agree” - was obtained for both, national variations and variations.
However, in question 5 only the Polish authority was mentioned as authority that does not follow the validation timeline in case of national variations.
With regard to validation of variations to MRP/DCP, only Portugal was identified as RMS that does not stick to the timelines and one more general complaint was received, that “there is often a delay (for weeks) of the official validation time before starting the variation procedures of Type IB and Type II.”
In terms of confidence in implicit approval of IB variations, only non-significant differences between national variations and variations were observed.

In order to investigate whether agencies are more complaisant if no CMS are involved, the questions on partial approval of IA variations were included in the survey. Only three participants experienced partial approval: one example with RMS Germany in a MRP and two examples for German national variations. No conclusions on different treatment can be drawn on this basis. Asked for any points, where the BfArM treats purely national MAs different than variations in MRP/DCP/CP, one answer stated that “in terms of purely national MA the BfArM seems to be more complaisantly; processing seems to be faster and grouping is handled more generously”. Unfortunately, only one more general statement was received on this question.
In conclusion, there is evidence that BfArM is accommodating and uses partial approvals of IA variations to avoid resubmissions. But on basis of the survey it cannot be determined whether there is any difference in treatment of variations and national variations.

As a matter of fact, national variations have the advantage that there is no delay possible due to waiting for any input of a CMS during dispatch, validation and assessment. In addition to this, the BfArM committed to follow strict timelines for validation and assessment, allows for generous grouping and offers the opportunity to submit completely paperless.[71] Furthermore, it is intended to apply reduced fees for national variations.[72]

Hence, it is appropriate to consider German national variations as advantaged compared to variations to MRP/DCP. It would be more than welcome if the positive approach of the BfArM served as a model for other member states. Extended to MRP/DCP, this approach would lead to an improved European variation system.

[71] Bekanntmachung über die Anzeige von Variations für rein nationale Zulassungen gemäß Kapitel IIa der Verordnung (EG) Nr. 1234/2008 ab dem 04.08.2013, die gemäß § 77 AMG in die Zuständigkeit des BfArM fallen vom 12. Juli 2013, http://www.bfarm.de/SharedDocs/Bekanntmachungen/DE/Arzneimittel/aender/bm-aender-20130712-Anzeige.pdf?__blob=publicationFile&v=4
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[72] BMG, AMGKostV, non-public draft of 30.01.2014, personal e-mail communication of Bundesverband der Arzneimittel-Hersteller e.V., (31.01.2014).

4 Conclusion and outlook

The former Classification Guideline has been revised thoroughly resulting in a new, updated Classification Guideline which is more comprehensive. Information formerly distributed over the Variations Regulation, Article 5 recommendations and best practice guides have now been combined for more facile use. As one of the major improvements, an opening clause was introduced, that allows the applicant to submit several minor changes under a higher procedure type, formerly known as “umbrella variation”. The revisions make the use of the new, updated Classification Guideline easier and more convenient in practice, especially for less experienced users. Nevertheless, there still seems to be some room for improvement. In addition, the awareness of the many positive aspects of the update, like amendments to IA variations to prevent resubmissions, seems to be still too low in practical use.

With the inclusion of the purely national marketing authorisations in the scope of the Variations Regulation, the various former national variation systems in the EU member states were replaced by the European variation system. For companies with many purely national MAs in different member states this results in saving time and money, easier variation tracking and reduced workload. Harmonised time lines and the fact that now the same core variation package can be used for the purely national MAs of the identical medicinal product in different member states are clearly a benefit.
In contrast, the benefits of the harmonisation do not take effect for companies which hold mainly German purely national MAs. Consequently, in this scenario the maintenance of purely national MAs has become more expensive, time consuming and complex.
According to the survey, overall workload and costs increased and no time is saved by the MAH due to inclusion of the German purely national MAs in the scope of the Variations Regulation. However, in general no compensation of this effects is intended by recruitment of additional staff or withdrawal of German purely national MAs. Depending on the features of the future, revised AMGKostV the statements on costs might need reassessment.

In practical use, some special cases occurred during the transition phase. Some issues were only temporary and applicants acted quickly to adapt to the new situation, for example by using new tools like CESP. Problems still occur in connection with submission of dossier updates and correction of errors in the dossier of purely national MAs.

The survey did not provide any indication that national variations are disadvantaged considering processing at the BfArM compared to MPR/DCP. On the contrary, in order to mitigate the transition to the European variation system, the BfArM developed a sophisticated system of status mails and remarkably facilitated horizontal and vertical grouping of variations to purely national MAs. At present, the awareness of the possibilities is still too low.

As not all possible changes to a MA are covered by the Variations Regulation, notifications of change according to Section 29(1) AMG will still remain necessary. Examples are transfer of a MA to a different legal entity, co-marketing issues and change in legal category. The handling of non-variations (changes in labelling or PL outside of the SmPC) and the national notification of pack sizes already approved in MRP/DCP are internally still under discussion at the BfArM.

The future challenge is to further improve the European variation system. It would be more than welcome if the positive approach of the BfArM in terms of variations to purely national MAs served as a model for other member states. Generous grouping, paperless submission, waiving of submission of original documents and immediate start of validation after receipt of a variation for all MRP/DCP could lead to a substantial reduction of workload for applicants and would accelerate the processes dramatically.
As seen in the survey, in case of optional submissions applicants weigh up costs and benefits carefully. To encourage the submission of general updates of the dossier, a European as well as a national approach is possible.
On the European level, the Classification Guideline could be amended with change categories typical for dossier updates such as IA variations for small corrections in the texts.
On the national German level, reduced fees in the range of IA variations could be set for IB variations that require only very little assessment. A first draft of the revised AMGKostV points in the same direction as it proposes reduced fees for very basic IA variations.
Likewise, for variations to MRP/DCP with RMS Germany and no CMS, the same fees as for national variations could be set, due to similar processing efforts.

A further improvement would be to allow the submission of conversion of dossiers from the former NTA format of 1998 to the current EU-CTD format along with any type II or IB variation that affects module 3 (former Part II) of the dossier.

Allowing simply more uploads in the PharmNet.Bund portal would save the applicants plenty of time and costs and avoid workarounds like CESP.

Eventually, status mails on positive closure could be sent to the applicants automatically after exceeding the respective timelines for IA and IB variations. This would give reassurance to applicants that do not feel comfortable to rely on implicit approval and would render variation tracking less important.

5 Summary

On 04.08.2013 the inclusion of the purely national MAs in the scope of Commission Regulation (EC) No 1234/2008, also known as ‘the Variations Regulation’, became effective together with the new, updated Classification Guideline of 16.05.2013. This thesis investigates the consequences of the related changes from an industrial point of view.
In a first step, the differences between the former and updated Classification Guideline were analysed. Secondly, differences between the former national German variation system and the European variation system as defined by the Variations Regulation and Classification Guideline were investigated. Subsequently, potential practical consequences of the differences found were drawn up. Lastly, in order to assess the potential consequences of the new regulatory situation, a survey was performed.

The new, updated Classification Guideline has been revised comprehensively and with due care. It contains an improved and comprehensive catalogue of change categories and it was amended with an opening clause for type II variations. This makes the use of the Classification Guideline easier and more convenient in practice. Nevertheless, there is still some room for improvement. For MA holders an increased awareness of the many positive aspects of the update would be beneficial in practical use.
Compared to the lean former national German variation system the European variation system is more laborious. Whereas for companies with many purely national MAs of identical medicinal products in different member states the use of the European variation system results in easier variation tracking and reduced workload, the benefits of the harmonisation do not take effect for companies, which hold mainly German purely national MAs. According to the survey, overall workload and costs increased and no time is saved by the MAH.

In order to mitigate the consequences of the transition to the European variation system, the BfArM developed a sophisticated system of status mails and remarkably facilitated horizontal and vertical grouping of variations to purely national MAs. Furthermore, a first draft of the revised AMGKostV suggests the reduction of fees for national variations in Germany.
Beyond this, reduced fees for IB variations that require only very little assessment should be considered to encourage the submission of general updates of the dossier.

Some transitional problems have been resolved, others are still open. A slight optimisation like allowing simply more uploads in the PharmNet.Bund portal would save the applicants plenty of time and costs and would avoid workarounds.
As not all possible changes to a MA are covered by the Variations Regulation, notifications of change according to Section 29(1) AMG will still remain necessary. In this respect, the handling of non-variations (changes in labelling or PL outside of the SmPC) and the national notification of pack sizes already approved in MRP/DCP are internally still under discussion at the BfArM.

To further improve the European variation system, the positive approach of the BfArM in terms of variations to purely national MAs should serve as a model for other member states.

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Annexes

Annex 1: Request to BfArM on category "B.V.c" of the Classification Guideline

Von: Winterscheid, Susanne
An: Loechner Klaus
Thema: AW: Anfrage zur Kategorie "B.V.c" in der Classification Guideline
Datum: Mittwoch, 22. Januar 2014 14:54:02

Sehr geehrter Herr Dr. Löchner,
vielen Dank für den Hinweis. Ich gehe davon aus, dass es sich um einen Fehler im Word-Dokument handelt, da es diese Kategorie auch im Index der entsprechenden pdf-Datei nicht mehr gibt. Auflagen müssen grundsätzlich gemäß der anderen Kategorien der Classification Guideline eingereicht werden.
Ich leite Ihren Hinweis zur Korrektur über die EMA an die EC weiter, nochmals vielen Dank.
Mit freundlichen Grüßen

Susanne Winterscheid

==========
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==========

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Bundesministeriums für Gesundheit / The BfArM is a Federal Institute
within the portfolio of the Federal Ministry of Health

Von: Loechner Klaus [KLoechner@betapharm.de]
Gesendet: Mittwoch, 22. Januar 2014 14:41
Bis: Winterscheid, Susanne
Betreff: Anfrage zur Kategorie "B.V.c" in der Classification Guideline

Sehr geehrte Frau Wiedemann,

im Rahmen meiner Masterarbeit für das DGRA-Studium untersuche ich die aktualisierte Classification Guideline vom 16.05.2013 (Guidelines C (2013) 2804), die seit dem 04.08.2013 in Kraft ist.

Bezüglich meiner Frage zur Kategorie "B.V.c" in der Classification Guideline hat man mich an Sie verwiesen:

In der aktuellen Classification Guideline vom 16.05.2013 (Guidelines C (2013) 2804) auf S. 32 im Index gibt es unter
B. Quality Changes
V. Changes to a marketing authorisation resulting from other regulatory procedures
den Punkt:
c) Other changes to the quality dossier requested by the competent authority

Dieser Punkt wird nur im Index des Annexes aber nicht in der folgenden Liste der Kategorien und auch nicht in der Liste im „Application form" erwähnt.

Kann diese Kategorie "B.V.c" zur Auflagenerfüllung verwendet werden oder handelt es sich lediglich um einen Fehler in der Classification Guideline?

Mit freundlichen Grüßen

Klaus Löchner

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Annex 2: Request to BfArM on grouping of IA variations

Von: Becker, Mariela
An: Loechner Klaus
Cc: Variation-grouping-request
Thema: AW: Anfrage zum Gruppieren von reinen IA-Variations, die beispielsweise im Rahmen eines "Annual review" eingereicht werden
Datum: Dienstag, 21. Januar 2014 17:35:19

Sehr geehrter Herr Loechner,

vielen Dank für Ihre heutige Anfrage.
Gerne möchten wir Ihnen dazu wie folgt antworten:

Gemäß Artikel 13d der Variation Regulation werden den nationalen Behörden für rein nationale Variations erweiterte Möglichkeiten zur Akzeptanz von Groupings eingeräumt. Die Regelungen, die für rein nationale Zulassungen in der Zuständigkeit des BfArM betroffen wurden, erläutert das BfArM in seiner Bekanntmachung vom 12.07.2013.

Die von Ihnen angeführte Einschränkung des BfArM, die in dieser Bekanntmachung aufgeführt ist, bezieht sich auf Artikel 13d Absatz 2c:

" Wird/werden dieselbe(n) Änderung(en) einer oder mehrerer Zulassungen ein und desselben Inhabers gleichzeitig bei derselben zuständigen Behörde eingereicht, fallen aber nicht unter Buchstaben a oder b, so können alle diese Änderungen dennoch in einer einzigen Einreichung zusammengefasst werden, sofern die zuständige Behörde mit einer solchen einzigen Einreichung einverstanden ist."

Für reine IA-Groupings gilt diese Einschränkung jedoch nicht, hier greift Artikel 13d Absatz 2a:

"Wird/werden dieselbe(n) geringfügige(n) Änderung(en) des Typs IA einer oder mehrerer Zulassungen ein und desselben Inhabers gleichzeitig derselben zuständigen Behörde mitgeteilt, können alle diese Änderungen in einer einzigen Mitteilung gemäß Artikel 13a erfasst werden."

Es ist demnach möglich, mehrere nationale Typ IA bzw. Typ IAIN Variations der Kategorien A, B und C in einem Grouping zusammenzufassen, auch wenn diese Änderungen nicht unmittelbar voneinander abhängen. Entsprechend ist die Bekanntmachung des BfArM so zu verstehen, dass die Einschränkung zur Kombination der Kat. B und C nur für Groupings gilt, die IB und/oder Typ II Variations beinhalten.

Ich gebe Ihnen recht dass die BfArM-Bekanntmachung an diesem Punkt spezifischer hätte formuliert werden können. Intern wurde bereit veranlasst, dass das BfArM in Kürze eine zusätzliche FAQ auf der externen BfArM-Homepage veröffentlicht, die dies eindeutig klarstellt.

Mit freundlichen Grüßen,
i.A.
Mariela Becker

Mariela Becker, M.D.R.A.

Leitung FG12 "Zulassung / Vereinfachten Verfahren I"
Head of unit 12 "licencing / simplified procedures I"
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Von: Loechner Klaus [mailto:KLoechner@betapharm.de]
Gesendet: Dienstag, 21. Januar 2014 09:07
An: Variation-grouping-request
Betreff: Anfrage zum Gruppieren von reinen IA-Variations, die beispielsweise im Rahmen eines "Annual review" eingereicht werden

Sehr geehrte Damen und Herren,

im Rahmen meiner Masterarbeit für das MDRA-Studium untersuche ich die Umsetzung der Verordnung (EG) Nr. 1234/2008 („Variation Regulation") für rein nationale zugelassene Arzneimittel. Dabei ist folgende Frage zum Grouping von „rein nationalen Variations" aufgekommen:

In der BfArM, „Bekanntmachung über die Anzeige von Variations für rein nationale Zulassungen gemäß Kapitel IIa der Verordnung (EG) Nr. 1234/2008 ab dem 04.08.2013, die gemäß § 77 AMG in die Zuständigkeit des BfArM fallen" vom 12. Juli 2013 werden unter Berufung auf Artikel 13d der Verordnung (EG) Nr. 1234/2008 großzügige generelle Regeln für das Gruppieren von Änderungen bei „rein nationalen Variations" festgelegt.

Allerdings wird das Grouping auch wie folgt eingeschränkt:
„Die Kombination aus Änderungen der Kapitel B) und C) ist nicht zulässig, es sei denn, diese Änderungen hängen unmittelbar voneinander ab."

Bezieht sich diese Einschränkung tatsächlich auch auf das Gruppieren von reinen IA-Variations, die beispielsweise im Rahmen eines „Annual Review" eingereicht werden?
Das würde bedeuten, das beim „Annual review" IA-Variations wie zum Beispiel
„A.5 Change in the name",
„B.II.e.7 Change in supplier of packaging components or devices a) Deletion of a supplier und
"C.I.9 c) Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes)

nicht miteinander kombiniert werden dürften.

Was wäre in diesem Fall die Rechtsgrundlage für die Einschränkung?

Oder dürfen weiterhin, wie in der Commission Regulation (EC) No 1234/2008 in der Fassung vom 4. August 2013, Artikel 13d, Abs. 2a vorgesehen, IA Variations der verschiedenen Kapitel A-D der Classification Guideline vom 16.05.2013 (Guidelines C (2013) 2804) miteinander kombiniert werden?

Mit freundlichen Grüßen

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Ust.-IdNr. DE155988224

Annex 3: Request to BfArM on national variations for a German MA within a MRP/DCP procedure

Von: Winterscheid, Susanne
An: Loechner Klaus
Thema: AW: Anfrage zur Anzeige von Packungsgrößen die bereits in den Verfahrenstexten genannt sind für Arzneimittel zugelassen im MR- bzw. DC-Verfahren
Datum: Donnerstag, 23. Januar 2014 19:08:47

Sehr geehrter Herr Dr. Löchner,
die Nennung der Packungsgrößen im § 29 AMG Abs. 2a betrifft nur die Arzneimittel, die nicht der Variation Regulation unterliegen. Alle Packungsgrößen, die in der SmPC noch nicht aufgeführt sind, müssen per Variation angezeigt werden. Die SmPC enthält in der Regel den Hinweis, dass nicht alle Packungsgrößen in allen member states vermarktet werden. Sollte sich der Vermarktungsstatus in Deutschland dann ändern, können Sie dies in einer nationalen Änderungsanzeige nach § 29 Abs. 1 anzeigen, die sich auf die Änderung der Texte und nicht die der Packungsgrößen bezieht. Diese fällt dann auch nicht unter die Zustimmungspflicht.
Mit freundlichen Grüßen

Susanne Winterscheid

==========
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Von: Loechner Klaus [KLoechner@betapharm.de]
Gesendet: Donnerstag, 23. Januar 2014 17:24
Bis: Winterscheid, Susanne
Betreff: Anfrage zur Anzeige von Packungsgrößen die bereits in den Verfahrenstexten genannt sind für Arzneimittel zugelassen im MR- bzw. DC-Verfahren

Sehr geehrte Frau Winterscheid,

darf ich mich noch mit einer weiteren Frage an Sie wenden?

Bei einigen MRP/DCP Verfahren werden nicht alle Packungsgrößen, die im Verfahren genehmigt wurden und die in den harmonisierten Texten enthalten sind, auch in den nationalen deutschen Texten genannt.

Wie ist eine Aufnahme dieser Packungsgrößen in die deutschen Texte anzuzeigen?

Vor dem 4. August 2013 wurde das über nationale Änderungsanzeigen gemeldet. Ich frage, weil seit 4. August 2013 in den mir bekannten Fällen (Klinikpackung sowie zusätzliche Packungsgröße wie im Verfahren gemeldet) die Einreichung einer **nationalen** Variation für die deutsche Zulassung innerhalb des DCP Verfahrens gefordert wurde unter Kategorie „B.II.e.5 Change in pack size of the finished product". Das hat den Vorteil, dass die Anzeige der Änderung nicht zustimmungspflichtig ist.

Dagegen wird im aktuellen Katalog der Änderungstatbestände (Stand: 08.11.2013 Version: 1.8) unter SKNR 0102 explizit auf Änderungen der Packungsgrößen in MRP/DCP Zulassungen eingegangen
(
http://www.bfarm.de/SharedDocs/Formulare/DE/Arzneimittel/Zulassung/aender/Katalogder%C3%84nderungstatbest%C3%A4ndeV18.pdf?__blob=publicationFile&v=3).
Diese Änderungsanzeige „Packungsgröße" gem. § 29 (1) AMG ist zustimmungspflichtig.
Die Zustimmungspflicht macht jedoch wenig Sinn, da die Packungsgröße ja bereits im MRP/DCP genehmigt wurde.

Wie ist denn die aktuelle Praxis und welche Überlegungen des BfArM stehen dahinter?

Mit freundlichen Grüßen nach Bonn

Klaus Löchner

From: Winterscheid, Susanne [mailto:Susanne.Winterscheid@bfarm.de]
Sent: Mittwoch, 22. Januar 2014 14:54
To: Loechner Klaus
Subject: AW: Anfrage zur Kategorie "B.V.c" in der Classification Guideline

Sehr geehrter Herr Dr. Löchner,
vielen Dank für den Hinweis. Ich gehe davon aus, dass es sich um einen Fehler im Word-Dokument handelt, da es diese Kategorie auch im Index der entsprechenden pdf-Datei nicht mehr gibt. Auflagen müssen grundsätzlich gemäß der anderen Kategorien der Classification Guideline eingereicht werden.
Ich leite Ihren Hinweis zur Korrektur über die EMA an die EC weiter, nochmals vielen Dank.
Mit freundlichen Grüßen

Susanne Winterscheid

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Annex 4: Questionnaire of the survey

Survey on the updated Classification Guideline for variations

Please state your name, company size and department:

Name	
Company size	☐ 1-100 employees ☐ 100-500 employees ☐ > 500 employees Optional: [company name]
Department	

This is a survey on the amended Commission Regulation (EC) No 1234/2008 (also known as the Variations Regulation) and the updated Classification Guideline[1] for variations, that became effective on August 4th 2013.

In addition to changed classifications, since August 4th 2013, most purely national German Marketing Authorisations (MA) are now under the scope of the Variations Regulation. As a result, since August 4th national variations have to be submitted instead of notification of change(s) ("Änderungsanzeige").

This questionnaire shall gather feedback and opinions on advantages and disadvantages of new or altered classifications of variations.

In addition, it shall investigate experiences with the national variations after inclusion of German purely national MAs in the scope of the Variations Regulation.

The goal of this survey is to perform an early assessment of the inclusion of the German purely national marketing authorisations in the scope of the Variations Regulation and the use of the updated Classification Guideline of 2013 in practice compared to the previous guideline and the former national German system, valid until October 2012.

Thank you for your participation!

[1] Guidelines of 16.05.2013 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.
This Guidelines replaced the former "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 (2010/C 17/01)"

Differences old/updated Classification Guideline

1. What did you expect from the updated Classification Guideline of 2013?
   [please type your answer here – just some bullet points]

2. What are your first experiences with the updated Classification Guideline for MRP/DCP/CP Marketing Authorisations (MA) (Advantages, Disadvantages, Problems)?
   [please type your answer here]

3. What are your first experiences with the updated Classification Guideline for use on purely national German MAs (Advantages, Disadvantages, Problems)?
   [please type your answer here]

4. What changes in classification are of advantage for you (e.g. graduated plans)?
   [please type your answer here]

5. The updated Classification Guideline stresses again the 7 day validation time for IB variations, only to be extended by 7 more days in case RMS desires upgrade from IB to type II and CMS are given this additional 7 days to agree/disagree. Do the agencies stick to this 7+7 days timeline?
   [please type your answer here]

6. For IB variations "The holder must wait a period of 30 days to ensure that the notification is deemed acceptable by the relevant authorities before implementing the change ("Tell, Wait and Do" procedure). Does this really work or do you wait for official approval of the RMS or national competent Agency?
   [please type your answer here]

7. Did you already or do you intend to use worksharing for any of your MRP/DCP MAs?
   [please type your answer here]

8. Did you already or do you intend to use worksharing for any of your purely national MAs?
   If yes, please indicate your motivation and planned amount of national worksharing submissions. If no, please indicate you motivation.
   [please type your answer here]

9. Do you intend or did you already use Art 5 procedure(s) since August 4th?
   If yes, due to national variations or MRP/DCP?
   [please type your answer here]

10. Did the BfArM ask for submission of national variations (e.g. for changes in indication, registered pack sizes) for a German MA within a MRP/DCP procedures?
    [please type your answer here]

11. Do you have cases, where the agency did not immediately rejected a IA variation due to missing documents but allowed to provide the missing documents during validation? If yes, which agencies were concerned and what kind of documents?
    [please type your answer here]

Differences updated Classification Guideline/former national German System

12. Please give your agreement/disagreement with below statements. Tick "5" for "I fully agree", "4" for "I partially agree", "3" for "undecided", "2" for "I mostly disagree" and "1" for "I do not agree":

Statements	1	2	3	4	5
The options for grouping were better in the former national German system compared to the Variations Regulation	☐	☐	☐	☐	☐
The options for worksharing are better in the Variations Regulation compared to former German national System	☐	☐	☐	☐	☐
It is good to have the option of submission of worksharing for purely national MAs	☐	☐	☐	☐	☐

13. Please tick the boxes as appropriate:

Statements	1	2	3	4	5
Complete adaptation to QRD-Template will now trigger an IB variation for purely national Mas, in case no other IB variation for texts is upcoming.					
Despite the costs, we will submit a complete adaption to QRD-Template in a separate IB variation	☐	☐	☐	☐	☐
We will include the standard sentence for side effects only to save costs	☐	☐	☐	☐	☐

14. With Variation Regulation becoming effective for purely national MAs, some useful change items were abandoned, e.g.

SKNR 1883 Results of stability testing of finished product without change in shelf-life
SKNR 4248 Adaption of texts to QRD-Template according toVersion 8 Rev. 2011
SKNR 1211 Fulfilment of conditions [Auflagenerfüllung]

What other change items that do not have an equivalent/counterpart in the Classification Guideline do you miss?
(Please compare with old former German national system, valid until October 2012.)
[please type your answer here]

15. Please give your agreement/disagreement with below statements. Tick "5" for "I fully agree", "4" for "I partially agree", "3" for "undecided", "2" for "I mostly disagree" and "1" for "I do not agree".

Statements	1	2	3	4	5
Due to the inclusion of German purely national MAs in the scope of the Variations Regulation…					
we save time	☐	☐	☐	☐	☐
the workload decreased	☐	☐	☐	☐	☐
we have to employ more people	☐	☐	☐	☐	☐
we will save costs	☐	☐	☐	☐	☐
the number of submissions increased	☐	☐	☐	☐	☐
variation tracking became easier	☐	☐	☐	☐	☐
the submission process is faster compared to former national German System	☐	☐	☐	☐	☐
we will withdraw German purely national MAs due to increased amount of work for maintenance	☐	☐	☐	☐	☐
we will withdraw German purely national MAs due to increased costs for maintenance	☐	☐	☐	☐	☐
we might have SCM issues/out of stock problems due to loss of former national tell-and-do variations	☐	☐	☐	☐	☐
it is difficult to submit an update of the dossier to current state of scientific and technical progress (e.g. inclusion of process validation protocols, stability data)	☐	☐	☐	☐	☐
it is more expensive to accomplish an update of the dossier to current state of scientific and technical progress (e.g. inclusion of process validation protocols, stability data)	☐	☐	☐	☐	☐

How did you deal with the transition?

16. Please give your agreement/disagreement with below statements. Tick "5" for "I fully agree", "4" for "I partially agree", "3" for "undecided", "2" for "I mostly disagree" and "1" for "I do not agree":

Statements	1	2	3	4	5
We have already started to work with the CESP-System (Common European Submission Platform) …					
to save time	☐	☐	☐	☐	☐
to save costs	☐	☐	☐	☐	☐
to speed up the submission process	☐	☐	☐	☐	☐
to upload more files than possible in PharmNet.Bund	☐	☐	☐	☐	☐
due to other reasons such as (please state)	☐	☐	☐	☐	☐

17. Please tick the boxes as appropriate:

Statements	more than 20	less than 20	less than 10	less than 5	no
We still have German purely national MAs that are not under the scope of the Variations Regulation:					
homeopathic medicinal products and traditional herbal medicinal products	☐	☐	☐	☐	☐
Marketing authorisations for Parallel import	☐	☐	☐	☐	☐
standardised marketing authorisations ("Standardzulassung")	☐	☐	☐	☐	☐
others: (Please give details)	☐	☐	☐	☐	☐

18. Do you have any paradox situations in your dossiers for purely national MAs, that cannot be solved with the Classification Guideline (e.g. a manufacturing site was notified in former German national system but no further work was done as required by classification guideline – how to submit missing documentation like process validation scheme or report?)
[please type your answer here]

19. Is the current PharmNet.Bund Adaption for submission of national Variations sufficient or which improvements are desired?
[please type your answer here]

Differences between variations in MRP/DCP and purely national MAs

20. Please give your agreement/disagreement with below statements. Tick "5" for "I fully agree", "4" for "I partially agree", "3" for "undecided", "2" for "I mostly disagree" and "1" for "I do not agree":

Statements	1	2	3	4	5
For submission and tracking of variations and national variations we follow the very same process.	☐	☐	☐	☐	☐
In spite of the fact that the national variations are now under the scope of the Variations Regulation, we feel that it is like a second national system due to the adaptions and national peculiarities like creation of procedure number and different importance of status mails.	☐	☐	☐	☐	☐
The options for grouping at BfArM are better for purely national German MAs than for MRP/DCP procedures	☐	☐	☐	☐	☐
In my experience, purely national variations are processed more slowly than MRP/DCP submissions.	☐	☐	☐	☐	☐
In my experience, variations to MRP/DCP procedures with RMS DE and no CMS are processed more slowly than MRP/DCP procedures with CMS.	☐	☐	☐	☐	☐
BfArM conforms to the deadlines for variations to MRP/DCP procedures with RMS DE and no CMS	☐	☐	☐	☐	☐
BfArM conforms to the deadlines for variations to MRP/DCP procedures with RMS DE and one or more CMS	☐	☐	☐	☐	☐
Validation and assessment of national variations at BfArM is according to the deadlines	☐	☐	☐	☐	☐
Validation and assessment of MRP/DCP variations at BfArM is according to the deadlines	☐	☐	☐	☐	☐
When grouping exclusively IA variations of a MRP/DCP procedure, did you experience restrictions to categories made by the RMS?	☐	☐	☐	☐	☐
When grouping exclusively IA variations of a purely national MAs did you experience restrictions to categories made by BfArM?	☐	☐	☐	☐	☐

21. Please give your agreement/disagreement with below statements. Tick "5" for "I fully agree", "4" for "I partially agree", "3" for "undecided", "2" for "I mostly disagree" and "1" for "I do not agree":

Statements	1	2	3	4	5
Implicit approval of IB variations works well for …					
purely national MAs at BfArM	☐	☐	☐	☐	☐
MRP/DCP submissions at BfArM as RMS	☐	☐	☐	☐	☐
MRP/DCP submissions at other RMS	☐	☐	☐	☐	☐

22. Did you experience any partial approvals of IA-variations for MRP/DCP procedures since 01/2010 (e.g. only a part of the submitted change in SmPC was approved)? If yes, who was the agency acting as RMS and did partial approvals save time or spare resubmission?
[please type your answer here]

23. Did you experience any partial approvals of IA-variations for purely national MAs since 08/2013? If yes, did partial approvals save time or spare resubmission?
[please type your answer here]

24. Are there any points, where the BfArM treats purely national MAs different than variations in MRP/DCP/CP?
[please type your answer here]

Annex 5: Tabulation of the survey outcome

Responses to open questions of the survey

1. What did you expect from the updated Classification Guideline of 2013?	Total votes	Comment
Improved and comprehensive catalogue of variation categories	4	
Harmonisation of requirements for purely national MAs in the EU	5	
Clarification on missing categories and closing of gaps	2	
Faster approval of variations in those countries which had not implemented the European variation sytem yet	1	
More precise definitions	1	
Inclusion of Article 5 recommendations	1	
Simplification of the variation procedures	1	
No expectations	1	
Own IA variation for editorial changes /dossier updates	1	
Reintroduction of the Umbrella Typ II Variation	1	
Not much	1	
No entry	1	

2. What are your first experiences with the updated Classification Guideline for MRP/DCP/CP Marketing Authorisations (MA) (Advantages, Disadvantages, Problems)?	Total votes	Comment
Some gaps in categorisation are closed but not all of them	4	
No relevant differences	1	
No problems so far	1	
No experience or not applicable	2	
There is often a delay (for weeks) of the official validation time before starting the variation procedures of Type IB and Type II. The consequence is an extension of the complete variation procedures.	1	belongs to question 5
Reduction of time, we have a lot of national MAs for the same Product.	1	evaluated under question 3
There are more classified changes now.	2	
No dramatic changes, except some additional conditions	1	
No entry	1	

3. What are your first experiences with the updated Classification Guideline for use on purely national German MAs (Advantages, Disadvantages, Problems)?	Total votes	Comment
Harmonised, common system for national and MRP/DCP is an advantage	3	
Clear classification/ clear requirements	3	
Higher costs in comparison to German national variation system	2	
Much less work / saves time in case of purely national MAs for same product in several countries	3	contains 1 question 4 and question 1 response
More administrative work	2	
National peculiarities are still not harmonised, such as the pack sizes	1	
Timelines clearly indicated (Day 0, 30, 60, 90)	1	
Harmonized and faster approval of variations which therefore can be implemented faster	1	moved from question 4
Disadvantage: submission of several, unconnected changes is more complicated than before	1	
More documents needed for submission - may lead to delays	1	
Disadvantage: less flexibility in Germany, but flexibility was already finished after the change of the German law before	1	
More time consuming. More complex.	1	

No problems	2	
No experience	2	
Not applicable	1	

4. What changes in classification are of advantage for you (e.g. graduated plans)?	Total votes	Comment
Some gaps in categorisation are closed	1	see question 2
Precise information on Ph. Eur. Updates	1	
More precise information about RMP-Updates	1	
Classification is now easier	1	
Some changes are new and useful (e.g. Ph.Eur. 2.9.40 to replace 2.9.5 or 2.9.6)	1	
No experience yet	1	
much less work, because of the fact that for all countries the same package of necessary documents can be prepared.	1	moved to question 3
harmonized and faster approval of variations which therefore can be implemented faster	1	moved to question 3
It is clear which documents have to submitted. At least for type IA and IB]	1	same participant mentioned this already in question
All IAIN that are now also applicable to national procedures	1	
According to EU regulations treatments for human diseases this had to be classified.	1	
Not applicable	2	
None discovered yet.	2	
Graduated plans are now IA	1	
No entry	1	

5. The updated Classification Guideline stresses again the 7 day validation time for IB variations, only to be extended by 7 more days in case RMS desires upgrade from IB to type II and CMS are given this additional 7 days to agree/disagree. Do the agencies stick to this 7+7 days timeline?	Total votes	Comment
No Information	1	rated as "not applicable"
No experiences so far	3	rated as "not applicable"
Not applicable	4	
Yes, if there is no need for providing the reasons for every single decision, this could speed up the time limits of answer.	1	rated as "yes"
Yes (currently)	1	rated as "yes"
By experience about ten days validation time for a IB variation	1	rated as "yes"
No experiences with MRP/DCP; CP: timelines are always followed very strict	1	
For purely national MAs: depends on the agency (e.g. HU yes, PL no)	1	
Yes for RMS DE, no for RMS PT	1	

6. For IB variations “The holder must wait a period of 30 days to ensure that the notification is deemed acceptable by the relevant authorities before implementing the change (“Tell, Wait and Do” procedure). Does this really work or do you wait for official approval of the RMS or national competent Agency?	Total votes	Comment
We are implementing after 30 days but there is still a uncertainty	1	rated as "yes"
Normally we do not wait for official approval, but some customers do	1	rated as "yes"
The experience shows: Most time it works, sometimes minor delays are possible.	1	rated as "yes"
Yes it works	2	rated as "yes"
No, we always wait for official approval of the NCA or of the RMS.	2	rated as "no"
It depends on the country. In the western European countries we wait until the period of 30 days are over and then implement, if there are no questions from the agency, in the eastern European countries we mostly wait until the official approval is given by the authority or we ask the affiliate if we can implement the change	1	rated as "no"
We wait for official approval to be on the safe side in case of release relevant variations.	1	rated as "no"
For purely national MAs: depends on the agency (e.g. HU yes, PL no)	1	rated as "no"
No Information, no entry or “not applicable”	4	
In summary:		
Yes it works	5	
No, uncertain or depending on RMS	5	
No Information, no entry or “not applicable”	4	

7. Did you already or do you intend to use worksharing for any of your MRP/DCP MAs?	Total votes	Comment
No	7	
No (did not come into consideration up to now)	1	rated as "no"
Not applicable	1	
Not applicable as we have almost only national Mas	1	
Yes	2	
Not yet, maybe in future.	1	
No entry	1	

8. Did you already or do you intend to use worksharing for any of your purely national MAs?	Total votes	Comment
No	9	
No (did not come into consideration up to now)	1	rated as "no"
Not planned so far	1	rated as "no"
Not yet, maybe in future. It depends on the intended variations and if worksharing will be an advantage for it.	1	
No entry	2	

9. Do you intend or did you already use Art 5 procedure(s) since August 4th? If yes, due to national variations or MRP/DCP?	Total votes	Comment
No information	1	
No	8	
No (did not come into consideration up to now)	1	rated as "no"
Yes, variation according §5 on a national basis	1	
No experiences so far	1	rated as "no"
Not yet, maybe in future.	1	
No, since the procedure is too timeconsuming	1	rated as "no"

10. Did the BfArM ask for submission of national variations (e.g. for changes in indication, registered pack sizes) for a German MA within a MRP/DCP procedures?	Total votes	Comment
No	3	
Yes	2	
Yes, for “Klinikpackungen” with the same size as the approved package size	1	rated as "yes"
Not applicable	5	
NO MRP/DCP in my company	1	rated as "not applicable"
Not until Sept 2013 – can’t tell what happened later	1	rated as "not applicable"
No entry	1	rated as "not applicable"

11. Do you have cases, where the agency did not immediately rejected a IA variation due to missing documents but allowed to provide the missing documents during validation? If yes, which agencies were concerned and what kind of documents?	Total votes	Comment
Yes, INFRAMED	1	
No	7	
No such case since years	1	rated as "no"
No cases	1	rated as "no"
No experience with this case so far	1	rated as "no"
Not applicable	2	
No entry	1	

14. With Variation Regulation becoming effective for purely national MAs, some useful change items were abandoned [...]. What other change items that do not have an equivalent/counterpart in the Classification Guideline do you miss?	Total votes	Comment
No entry	4	
No experiences	1	
Not applicable	4	
None	1	
1763 redaktionelle Änderung (editorial change)	1	
We definitely miss an adequate system to correct smaller issues to the texts (PIL/SmPC) in case of faults or mistakes without having a Type IB variation.	2	
0204 Information and documents about analytical testing	1	
I miss the listed ones too (1882, 4248, 1211)	1	

18. Do you have any paradox situations in your dossiers for purely national MAs, that cannot be solved with the Classification Guideline	Total votes	Comment
No	5	
Not applicable	2	
No entry	2	rated as "not applicable"
Yes, to be solved with IB-variations	1	
Yes, we have those situations especially when it comes to manufacturers	1	
For example: Submission of stability data without extension of shelf life. There is no possibility for a submission of follow-up stability data after completion of stability studies based on the post-approval stability commitment.	1	rated as "yes"
Main problem is correction of errors in the dossier and dossier update. Switch from NtA format to CTD requires many variations that are not classified ASMF update requires many variations that are not classified if you want to avoid a type II variation	1	rated as "yes"
IB z) variations solve all problems	1	

19. Is the current PharmNet.Bund Adaption for submission of national Variations sufficient or which improvements are desired?	Total votes	Comment
Yes/sufficient	4	
More space for more files needed	1	
No, it is a disadvantage that only few files can be uploaded as attachments. Therefore an additional submission via CESP and time for its submission are necessary.	1	rated as “More space for more files needed”
Sufficient in combination with CESP	1	rated as “More space for more files needed”
No experiences	2	
The system was not tested yet as we still use DVD+paper submission.	1	rated as "no experiences"
No current experiences	1	rated as "no experiences"
No experiences so far	1	rated as "no experiences"
Can’t tell.	1	rated as "no experiences"
No entry	1	

22. Did you experience any partial approvals of IA-variations for MRP/DCP procedures since 01/2010 (e.g. only a part of the submitted change in SmPC was approved)?	Total votes	Comment
No	6	
Not yet	1	rated as "no"
Not yet	1	rated as "no"
Can’t remember	1	rated as "no"
Yes, it was a grouped variation concerning issues of the prior DDPS. No resubmission was required. The subject was resolved by the new submission of the current summary of the Pharmacovigilance Master File (PSMF). It was a MRP- DE: RMS and three additional CMSs.	1	
Not applicable	2	
No MRP/DCP in this Company	1	rated as "not applicable"
No entry	1	

23. Did you experience any partial approvals of IA-variations for purely national MAs since 08/2013? If yes, did partial approvals save time or spare resubmission?	Total votes	Comment
Yes, due to lack of experience in how to use the Variations Regulation for national variations in the beginning	1	
Yes, editorial changes in texts submitted along with IA were not accepted; resubmission along with next IB	1	
Not yet	2	rated as "no"
No	4	
No partial approval so far	1	rated as "no"
Not since 08/2013	1	rated as "no"
Not applicable	1	
No experience	1	rated as "not applicable"
No entry	2	

24. Are there any points, where the BfArM treats purely national MAs different than variations in MRP/DCP/CP?	Total votes	Comment
No	2	
Not as far as I know	1	rated as "no"
Not applicable	3	
No experience until now	1	
No experience	1	
No experiences so far	1	
Can’t tell.	1	rated as "not applicable"
In terms of purely national MA the BfArM seems to be more complaisantly; processing seems to be faster and grouping is handled more generously	1	
Nevermind! Before the implementation of the updated Classifiaction Guideline in Germany the variation system was easy to handle, proved high efficacy, and needed less bureaucracy. BfArM’s principle based on the legal self-responsibility of the MAH and defined list of major variations. The rest were just barely notifications. That meant that the approval of approval procedures had to be expected after 3 months. Then the advantage for Germany was to achieving a EU system that is simple as the German national system.	1	
No entry	2	

Responses to questions with tick boxes

Questions

12. Level of agreement

Statements	1	2	3	4	5	Abstention	Sum	Total votes	Av rate
The options for grouping were better in the former national German system compared to the Variations Regulation	4	2	2		6		44	14	3.14
The options for worksharing are better in the Variations Regulation compared to former German national System		1	6	3	4		52	14	3.71
It is good to have the option of submission of worksharing for purely national MAs	1	1	3	2	7		55	14	3.93

13. Level of agreement

Statements	1	2	3	4	5	Abstention	Sum	Total votes	Av rate
Complete adaptation to QRD-Template will now trigger an IB variation for purely national MAs, in case no other IB variation for texts is upcoming.									
Despite the costs, we will submit a complete adaption to QRD-Template in a separate IB variation	2	3	1	1	3	4	30	10	3.00
We will include the standard sentence for side effects only to save costs	2	1	2	3	1	5	27	9	3.00

15. Level of agreement

Statements	1	2	3	4	5	Abstention	Sum	Total votes	Av rate
Due to the inclusion of German purely national MAs in the scope of the Variations Regulation…									
we save time	2	7	3		2		35	14	2.50
the workload decreased	4	4	3	1	2		35	14	2.50
we have to employ more people	5		5	1	1	2	29	12	2.42
we will save costs	5	2	4	1	2		35	14	2.50
the number of submissions increased	1	1	6	3	2	1	43	13	3.31
variation tracking became easier	1	3	3	2	4	1	44	13	3.38
the submission process is faster compared to former national German System	3	3	6		1	1	32	13	2.46
we will withdraw German purely national MAs due to increased amount of work for maintenance	8	1	1	1	1	2	22	12	1.83
we will withdraw German purely national MAs due to increased costs for maintenance	8	1	1	1	1	2	22	12	1.83
we might have SCM issues/out of stock problems due to loss of former national tell-and-do variations	3	4	1	2		4	22	10	2.20
it is difficult to submit an update of the dossier to current state of scientific and technical progress (e.g. inclusion of process validation protocols, stability data)	3	2	1	4	4		46	14	3.29

Statements	1	2	3	4	5	Abstention	Sum	Total votes	Av rate
it is more expensive to accomplish an update of the dossier to current state of scientific and technical progress (e.g. inclusion of process validation protocols, stability data)	3	1	3	2	5		47	14	3.36

16. Level of agreement

Statements	1	2	3	4	5	Abstention	Sum	Total votes	Av rate
We have already started to work with the CESP-System (Common European Submission Platform) …									
to save time		1	1	2	7	3	48	11	4.36
to save costs		1		2	8	3	50	11	4.55
to speed up the submission process	1	2		1	7	3	44	11	4.00
to upload more files than possible in PharmNet.Bund	2				8	4	42	10	4.20
due to other reasons such as (please state)	2		1			11	5	3	1.67

17. Amount of MAs

Statements	More than 20	Less than 20	Less than 10	Less than 5	No	No entry	Total votes
We still have German purely national MAs that are not under the scope of the Variations Regulation:							
homeopathic medicinal products and traditional herbal medicinal products	1		2		9	2	12
Marketing authorisations for Parallel import	1			1	9	3	11
standardised marketing authorisations ("Standardzulassung")	1	1		3	6	3	11
others:(Please give details)	1				3	10	4

Combined data from question 15 and 17:

Participant	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Amount of German purely national MAs that are not under the scope of the Variations Regulation	More than 20	More than 20	Less than 20	Less than 10	Less than 5	Less than 5	Less than 5	0	0	0	0	0	Not known	Not known
we save time	3	5	2	2	3	1	2	2	2	2	5	1	2	3
the workload decreased	2	5	4	1	3	1	2	2	2	3	5	1	1	3
we will save costs	2	5	3	1	3	2	3	1	4	5	3	1	1	1
Average rate	**3.67**		**3.00**	**1.33**	**2.22**			**2.38**						

20.	**Level of agreement**								
Statements	1	2	3	4	5	Abstention	Sum	Total votes	Av rate
For submission and tracking of variations and national variations we follow the very same process.	2	2	1	3	5	1	46	13	3.54
In spite of the fact that the national variations are now under the scope of the Variations Regulation, we feel that it is like a second national system due to the adaptions and national peculiarities like creation of procedure number and different importance of status mails.	3	2	4	2	2	1	37	13	2.85
The options for grouping at BfArM are better for purely national German MAs than for MRP/DCP procedures.	1	1	9	1	1	1	39	13	3.00
In my experience, purely national variations are processed more slowly than MRP/DCP submissions.	3	1	5	3	2		42	14	3.00
In my experience, variations to MRP/DCP procedures with RMS DE and no CMS are processed more slowly than MRP/DCP procedures with CMS.	1	3	5	1	1	3	31	11	2.82
BfArM conforms to the deadlines for variations to MRP/DCP procedures with RMS DE and no CMS.	1		8	2	1	2	38	12	3.17
BfArM conforms to the deadlines for variations to MRP/DCP procedures with RMS DE and one or more CMS.			8	2	2	2	42	12	3.50
Validation and assessment of national variations at BfArM is according to the deadlines.	1		6	4	2	1	45	13	3.46
Validation and assessment of MRP/DCP variations at BfArM is according to the deadlines.		1	6	3	2	2	42	12	3.50
When grouping exclusively IA variations of a MRP/DCP procedure, did you experience restrictions to categories made by the RMS?	2	1	8	1		2	32	12	2.67
When grouping exclusively IA variations of a purely national MAs did you experience restrictions to categories made by BfArM?	3	2	6	1		2	29	12	2.42

21.	**Level of agreement**								
Statements	1	2	3	4	5	Abstention	Sum	Total votes	Av rate
Implicit approval of IB variations works well for …									
purely national MAs at BfArM	1	1	5	1	3	3	37	11	3.36
MRP/DCP submissions at BfArM as RMS			7		3	4	36	10	3.60
MRP/DCP submissions at other RMS			9		2	3	37	11	3.36

Annex 6: List of deleted Article 5 recommendations

No.	Article 5 reccomendation	Current classification	Article 5 variation type	variation type	Date	Summary of the proposed change
1	B.I.a.1.z	B.I.a.1.h	IB	IB	26.04.2010	Add an alternative sterilisation (gamma irradiation) site for the active substance.
2	B.I.d.z	B.I.d.c	IB	IA or IB if with reduction of frequency	25.07.2011	Deletion of tests or reduction in the frequency of testing in a previously approved stability protocol of the active substance
3	B.I.z	B.II.h.1.a	II	II	20.12.2010	To update section 3.2.A.2 “Adventitious Agents Safety Evaluation” with the introduction of new viral and/or non viral validation studies: Studies related to manufacturing steps investigated for the first time on one or more pathogens, with or without modifications of risk assessment (according to the guideline CPMP/BWP/65180/03), with or without modifications of the Summary of Product Characteristics
4	B.I.z	B.II.h.1.b.1	II	II	20.12.2010	To update section 3.2.A.2 “Adventitious Agents Safety Evaluation” with the introduction of new viral and/or non viral validation studies Studies to replace obsolete studies already reported in the dossier (as scientific experience accumulates, studies could require re-examination to ensure that they remain of an acceptable standard), on the same pathogens, with modifications of risk assessment and with modifications of the Summary of Product Characteristics
5	B.I.z	B.II.h.1.b.1	II	II	20.12.2010	To update section 3.2.A.2 “Adventitious Agents Safety Evaluation” with the introduction of new viral and/or non viral validation studies Studies to replace obsolete studies on the same pathogens, already reported in the dossier, with modifications of risk assessment, without modifications of the Summary of Product Characteristics
6	B.I.z	B.II.h.1.b.2	IB	IB	20.12.2010	To update section 3.2.A.2 “Adventitious Agents Safety Evaluation” with the introduction of new viral and/or non viral validation studies Studies to replace obsolete studies on the same pathogens, already reported in the dossier, without modifications of risk assessment, without modifications of the Summary of Product Characteristics
7	B.I.z	B.II.h.1.b.2	IB	IB	20.12.2010	To update section 3.2.A.2 “Adventitious Agents Safety Evaluation” with the introduction of new viral and/or non viral validation studies Robustness studies on already investigated step(s) without modifications of the risk assessment and without modifications of the Summary of Product Characteristics
8	B II.a.1.a	B II.a.1.a	IAIN	IAIN if differentiation of strength is given (condition 4)	18.04.2011	Removal of imprints from tablets

9	B.II.a.2.z	B.II.a.2.c	II	II	28.06.2010	Change in the shape or dimensions of the pharmaceutical form: Addition of a second kit for radiopharmaceutical preparation with another fill volume
10	B.II.b.3.z	B.II.b.3.a	IB	IB for modified release (condition 2)	22.03.2010	Change in the manufacturing process of the finished product: minor change in the manufacturing process of modified release oral dosage form.
11	B.II.b.3.z	B.II.b.3.a	IB	IB for solution for injection (condition 2)	26.04.2010	Change in the manufacturing process of the finished product: minor change in the manufacturing process of solution for injection/infusion.
12	B.II.c.1.z	B.II.c.1.g	IB	IB	22.03.2010	Change in specification of the excipient Maltose from in-house to USP monograph (Maltose monohydrate). LAL test will continue to be carried out as additional specification as required by the monograph of the Ph.Eur.
13	B.II.d.1.a	B.II.d.1.h	IA	IAIN	20.12.2010	Update of the dossier to comply with the provisions of a general monograph for the test of a finished product of the Ph.Eur. – Tightening of specification limits
14	B.II.d.1.z	B.II.d.1.i	IB	IA IB when switching to uniformity of mass	22.11.2010	Ph.Eur. 2.9.40 Uniformity of Dosage Units is introduced to replace the current method Ph.Eur. 2.9.6 Uniformity of Content.
15	B.II.d.1.z	B.II.d.1.i	IB	IA	20.12.2010	Ph. Eur. 2.9.40 Uniformity of dosage units (by mass variation) is introduced to replace the current method Ph. Eur. 2.9.5 Uniformity of mass. Please note that new specification (test and limits) should be introduced
16	B.II.f.1.z	B.II.f.1.e	IB	IA if condition 2 is fulfilled - no widening of specifications, removal of stability indicating parameters or reduction of testing frequency)	24.01.2011	Change of stability protocol for annual stability
17	C.I.z.	C.I.8	IAIN	IAIN	25.06.2012	Introduction or change of the summary of Pharmacovigilance System
18	C.I.z.	C.I.8	IAIN	IAIN	25.06.2012	Changes in the QPPV, including contact details, and/or the location of the PSMF as part of the summary of the pharmacovigilance system for medicinal products for human use can be submitted as type IAIN variation according to classification category C.I.z (See also the EC classification guideline for public consultation: http://ec.europa.eu/health/files/betterreg/2012_06_11_public_consultation_en.pdf) Please not that this recommendation will be updated as soon as art 57 database is functional
19	C.I.z	C.I.10 human and C.II.8 veterinary	IAIN	IAIN	19.11.2012	Change in frequency and / or date of submission of periodic safety update reports (PSUR)

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

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Dr. Klaus Löchner