The end of an era:
Implementing Variation Directive 2009/53/EC into German Drug Law

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1 LIST OF ABBREVIATIONS

AM	Amendment
AMG	Arzneimittelgesetz (Medicinal Products Act - The Drug Law)
AMIS	Arzneimittelinformationssystem (Drug information system)
ATC	Anatomical Therapeutic Chemical (Classification System)
BAnz	Bundesanzeiger
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BGBl	Bundesgesetzblatt (Federal Gazette)
BVL	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (Federal Office of Consumer Protection and Food Safety)
CMDh/ v	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human / Veterinary
CP	Centralised Procedure
CSP	Core Safety Profile
DCP	Decentralised Procedure
DDPS	Detailed Description of the Pharmacovigilance System
EA	Extension Application
EC	European Commission
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEC	European Economic Community
GMP	Good Manufacturing Practice
HMA	Heads of Medicines Agencies
MA	Marketing authorisation
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MHRA	Medicines and Healthcare products Regulatory Agency
MRP	Mutual Recognition Procedure
No	number
OJ	Official Journal
PE	Pharmaceutical entrepreneur
PEI	Paul-Ehrlich-Institut
PIL	Patient Information Leaflet
PSUR	Periodic Safety Update Report
SmPC	Summary of Product Characteristics
USR	Urgent Safety Restriction
vs.	versus
WSP	Work Sharing Procedure

Note: References to “Section 29” relate to the AMG and references to “Annex I” or “Annex II” relate to Regulation 1234/2008/EC if not given otherwise.

2 INTRODUCTION

2.1 THE EVOLUTION OF SECTION 29 OF THE GERMAN MEDICINAL PRODUCTS ACT

The provisions currently in force concerning changes to existing, national marketing authorisations (MA) in Germany are the result of an evolutionary process.

Its development started with the second Drug Law adopted in August, 24th, 1976[1] as the late transposition of Council Directive 65/65/EEC[2] into national law. The complete revision of the Drug Law had become necessary and was deeply inspired by the thalidomide (Contergan®) tragedy which had reached its climax in 1961.

At the time of the start of marketing of Contergan® on October 1st, 1957[3], there were no appropriate provisions in place to protect unborn children from the teratogenic and neuropathic effects of the active substance thalidomide. At that time, the marketing of a medicinal product required no prior scientific assessment or approval from the side of the authorities.

This was not changed when on May 16th, 1961 a comprehensive review of the relevant legislation was adopted to substitute the provisions in place[4]. The publishing date of the law was a mere coincidence and stood in no relationship with unfolding events leading to the marketing stop of Contergan® on November 26th, 1961 by Grünenthal[3]. In line with the drug law as adopted on May16th, 1961, medicinal products were simply registered. The responsibility for conducting appropriate testing still rested solely on the pharmaceutical entrepreneur (PE).

Similar to the registration itself, it was laid down in Section 23 of this first Drug Law that changes to the registration had to be submitted without delay to the competent authority, the German health authority[i] at that time.

This concerned changes to

- the company, name and address of the applicant,
- the claimed indications including contra-indications,
- the package leaflet,
- the registered pack sizes and
- the composition with respect to the excipients.

A new registration had to be submitted for the following changes:

- change to the name of the medicinal product,
- change to the composition of the medicinal product by type and quantity with respect to the active substance,
- change of the pharmaceutical form.

With the new legislation entering into force in January 1st, 1978 a paradigm shift took place. The former registration of a new medicinal product was supplanted by the requirement to apply for a marketing authorisation (MA). The application now needed to be substantiated by the applicant

[i] Bundesgesundheitsamt (BGA)

with documentation according to Sections 22 to 24 aimed at proving the quality, safety and efficacy of the medicinal product.
In consequence, the competent authority was now equipped with the legal means to assess the submitted documentation and reject applications on justified grounds.

Whereas a completely new application and assessment process was created for obtaining a MA, there were no substantial alterations to the way changes were to be brought to the attention of the competent authority. The requirements to apply for changes to the MA were laid down in Section 29. In the current version of the German Drug Law (AMG), this section is still to be consulted with regards to performing changes to existing MAs. Yet in its first installment, Section 29 very much resembled its predecessor. In case of changes to the documentation as detailed in Sections 22 to 24 AMG, the competent higher federal authority was still to be notified without delay. Since the requirements to the submitted documentation had been extended significantly, this resulted in an increase of changes to be applied for.

Due to the change of the form of application (registration vs. required approval in the form of a MA), the change in the name of the product was reduced to an administrative change. It now only required an update of the license as opposed to a new registration further to Section 29(2).

The remaining cases in which a new registration application had to be submitted were amended with the following changes pursuant to Section 29(3):

- extension of the approved indications,
- change in the manufacture of sera, vaccines and test allergens,
- reduction of the withdrawal period for veterinary medicinal products.

But still, with the exception of changes which required new applications, no hurdle as to when the change may be applied was set ("tell and do" concept). Such a restriction to implementing changes was only introduced with the 2nd amendment to the AMG which entered into force on February 1st, 1987.

In the newly created sub-section 29(2a) it was stated that the following changes required approval by the competent federal authority prior to implementation by the applicant:

- a change in posology,
- a change of method and duration of administration and
- a restriction of contra-indications, side-effects or interactions with other substances.

Also, any change to the approved pack sizes now belonged to this novel "tell, wait and do" category and was exempt from the requirement to submit a new application.

The changes as listed in section 29(2a) may be implemented in the labelling, package leaflet and the expert information[ii] in case the higher competent authority did not object to the application within 3 months thereby approving the change implicitly. The time frame as established with this amendment was not changed with subsequent revisions of the Drug Law and remains in effect.

Apart from those changes, the requirements for pharmacovigilance notifications on observed side-effects, interactions with other substances e.g. were included in section 29(1) with this amendment. Over time, the section was revised a number of times. Yet, with the 12th amendment to the Drug Law coming into effect August 6th, 2004, the section on pharmacovigilance issues

[ii] Fachinformation

was moved to the newly created section 63b. Since the focus of this work is on national variations and not pharmacovigilance, it shall not be detailed further.

With the described 2nd amendment to the AMG and as early as 1987, the general frame work to conducting national variations was laid down in national legislation.
It consists of three types of change categories which remain current and in effect:

- changes not requiring prior approval[iii],
- changes requiring prior approval[iv],
- changes requiring the submission of a new marketing authorisation application (MAA).

With subsequent amendments to the AMG, new types of changes were introduced, categorisations changed, requirements detailed or clarifications added. These revisions concerned only the change categories requiring prior implicit approval or necessitating the submission of a new MAA as detailed requirements were only laid down for those two categories.

These changes to the legislation up to the 14th amendment are presented in an overview in Table **1** below.

AM no.	Entry into force	PA	nMAA	Section 29	Notable changes introduced with the amendment
4	20.4.1990	-	-	2a(1)	Clarification that the prior approval regarding the safety relevant aspects applies for prescription medicinal products only
		-	X	2a(2) 2a(3)	Clarification and categorisation as requiring pre-approval in the case of – a change in composition with regard to active substances, excluding the medically active constituents or – a conversion into a pharmaceutical form which is comparable to the one authorised for marketing.
		-	X	3(3a)	Introduction of genetic engineering technology
		X	-	2a(4)	Any changes *in manufacturing procedures using genetic engineering technology*
5	17.08.1994	-	X	3(4)	Change in the manufacture of preparations derived from blood
		-	-	3	Clarification that in general the decision on the requirement to apply for a new MA is reached by the competent higher authority.
7	04.03.1998	-	-	4	Inclusion of reference on current legislation concerning MAs authorized in the Centralised and Decentralised[v] Procedures

[iii] nicht zustimmungspflichtige Änderungsanzeigen
[iv] zustimmungspflichtige Änderungsanzeigen
[v] renamed as Mutual Recognition Procedure

AM no.	Entry into force	PA	nMAA	Section 29	Notable changes introduced with the amendment
8	11.9.1998	X	-	2a(1)	Clarification and categorisation as a change requiring prior approval instead of a new MAA in case of indications belonging to the initially authorised area of therapy
		X	-	2a(3a)	Introduction of *treatment with ionising radiation*
		X	-	2a(4)	Re-classification of application for a change in the manufacturing *for sera, vaccines, preparations derived from blood, test allergens, test sera and test antigens*
		X	-	2a(4)	Introduction of changes in the testing procedures or application of a longer shelf-life for sera, vaccines, preparations derived from blood, test allergens, test sera and test antigens
10	12.7.2000	-	-	2a(1)	Clarification in wording that only an *addition or modification of an indication which is to be classified under another area of therapy* leads to the requirement to apply for a new MA.
12	06.8.2004	X	-	2a(6)	Addition of changes concerning the withdrawal period as laid down in Regulation (EEC) No. 2377/90 or in case the withdrawal period-determining component of a fixed combination is no longer contained in the medicinal product
		-	X	3(5)	Amendment to consider the exceptions concerning changes of the withdrawal period pursuant to sub-section 2a(6)
		-	-	5	Update of reference to current legislation (Commission Regulation (EC) No 1084/2003) for MAs approved under the Mutual Recognition Procedure
14	06.09.2005	-	-	1b-1d	Notification requirements pertaining to the newly introduced “Sunset Clause”
		X	-	2a	Clarification that sub-section 2a also applies for the extension of the target species in the case of medicinal products not intended for use in food-producing animals
		-	-	4	Update of reference to current legislation for MAs approved under the CP

Table 1: Notable Revisions of Section 29 AMG
Please note: Amendments not listed did not contain changes to Section 29
Abbreviations: AM no. – Amendment number, nMAA – new Marketing Authorisation Application, PA – change requiring prior approval.

2.2 LEGAL BASICS OF CHANGES TO EUROPEAN MARKETING AUTHORISATIONS

For a long time, the regulation of medicinal products was a purely national business. This changed with the adoption of Council Directive 65/65/EEC[2] laying down the basic rules for MAAs in the Member States.
The idea to introduce common European rules was borne as a reaction to the thalidomide scandal which exerted great influence in shaping the wording and content of the Directive. It was stated in the preamble to the directive that *the primary purpose of any rules concerning the production and distribution of proprietary medicinal products must be to safeguard public health*. Furthermore, it was the understanding that trade hindrances due to diverging *national provisions* had to be overcome in order to promote a common market.

With Council Directive 65/65/EEC the documentation requirements to submitting a MAA were extended and detailed. The transition period to implementing the directive into national law was five years. As detailed in the chapter before, the submission of MAAs became compulsory in Germany only when the second Drug Law came into effect in 1978. With this, the Member State was late to implement the provisions into national law.

Still, these basic rules were designed for the national level and did not contain any provisions to perform variations to the authorisations. Hence, no harmonised procedures went into effect at that time. Later there were attempts at creating European procedures for MAAs, though, by establishing the non-mandatory Multi-State Procedure[5,6] which coordinated a number of simultaneous national applications in the Member States. Following authorisation the procedure was also to be used for variations to the Summary of Product Characteristics (SmPC) in order to maintain harmonisation of the document.

This was followed by the creation of the Concertation Procedure for high-technology, e.g. biotechnology medicinal products[7]. Both procedures did not allow for a true collaboration on the European level since in case of objections, the opinions of the Committee for Proprietary Medicinal Products (CPMP) as established by Directive 75/319/EEC[5] were not legally binding for the Member States. Recommendations in nature, no harmonised decisions on the applications were taken.

This changed on January 1st, 1995 when both the Mutual Recognition Procedure (MRP)[vi] and Centralised Procedure (CP) were introduced for obtaining MAs in more than one Member State[8,9]. In both Directive 95/39/EEC and Regulation (EEC) No 2309/93, a provision was included assigning the European Commission (EC) and the European Agency for the Evaluation of Medicinal Products ("the Agency") the task on drawing up *appropriate arrangements for the examination of variations to the terms of a marketing authorization.* Owing to the differences in the procedures as well as references to legislation, those took the form of the two Regulations (EC) No 541/95[10] and 542/95[11] for medicinal products authorised by way of the MRP and CP, respectively. Both regulations came into force on March 14th, 1995.

In these regulations, a harmonised system for performing variations for multi-national procedures was laid down. Changes to MAs were categorised as "minor variations" (Type I),

[vi] initially named Decentralised Procedure

major variations (Type II) as well as changes according to Annex II of the named regulations necessitating a new MAA. Each change was to be submitted as a single application. An exception was to be made in the case of consequential changes for which a detailed justification was to be submitted with the application[vii].

The definitions for classification of a change as a Type I variation were included in Annex I to the regulations. Therein, the conditions to be fulfilled for classification as a minor variation were listed. Consequently, in case the conditions set forth could not be fulfilled, the change was automatically to be classified as major Type II variation.

The burden of the assessment of the variation application is to be shouldered by the Reference Member State (RMS) and the Agency in the case of the MRP and CP, respectively. Especially in the former procedure, this was deemed necessary to avoid duplicitous work on the part of the authorities in the Member States involved.

Since major variations were expected to require a more detailed and thorough assessment by the authorities, a time frame of 60 days was set as opposed to the shorter 30 days for minor variations. Furthering the cause of improving safety of medicinal products, the approval of Type II variations is always explicit. In effect, the MAH cannot implement the changes without the expressed approval from the RMS or the Agency. For Type I variations an implicit approval is possible.

	Type I	**Type II**
Approval	implicit	explicit
Time frame	30 days	60 days
Classification given	yes	no

Table 2: Main features of the types of variations as introduced by Regulations 541/95/EC and 542/95/EC

In accordance with the provisions of Article 15c number 2 of Council Directive 93/39/EEC and Article 71 of Regulation (EEC) No 2309/93, the operation of and experience with the procedures were to be reviewed by the EC by January 1st, 2001.
As a result of this detailed review, the legislation on performing variations was updated with Commission Regulation (EC) No 1084/2003[12] and 1085/2003[13] repealing the legislation formerly in place. Both regulations entered into force on October 1st, 2003.

In general, the system and principles as established with Regulations 541/95/EC and 542/95/EC were deemed to be appropriate for performing variations. At the same time, the requirement to simplify the procedures in place and to tighten the time-frames had become apparent. The intended improvement was to be achieved by introducing an additional, more simplified procedure. By definition, this procedure was restricted to variations that were minor in nature. Consequently, it was also assigned to category of Type I leading to a split-up between the new Type IA and Type IB (= former Type I) variations. As before, special conditions as layed down in Annex I of the regulations were to be fulfilled in order to meet

[vii] Article 4 of both Regulation (EC) No 541/95 and 542/95

the classification as a minor variation. The valid submission for a Type IA variation was to be acknowledged within 14 days.

For the category of major Type II variations, it was made clear, that the assigned time frame of 60 days may be shortened to 30 days or lengthened to 90 days as appropriate. The rationale behind this was a flexibilisation of the system in order to be able to react quickly e.g. to new safety information or be able to thoroughly assess the documentation e.g. for the change or addition of therapeutic indications.

In the former instance, an even speedier procedure had already been put into place with the urgent safety restriction (USR)[viii], but no details on the procedure to be followed had previously been laid down. This was clarified in Article 9 of the new provisions. In case of an *event of risk to public or animal health* an interim change to the SmPC[ix] could be effected if no objection was received from a Member State within 24 hours. By itself, the USR is not a type of variation, though. Instead it serves as measure to implement safety changes to the SmPC without delay. A variation to approve the changes is to be submitted within 15 days of the USR with the type of variation to be discussed with the RMS or the Agency.

Further special procedures were introduced for human influenza vaccines (Article 7) and in case of a pandemic situation with respect to human diseases (Article 8).

With the subdivision of the Type I category of variations, Annex I containing the definitions and conditions for such variations had consequently to be revised. The opportunity was also taken to extend the list of minor variations not foreseen previously in order to reduce the work load for both applicants and authorities.

Changes were also made with respect to the requirement to submit a new MAA in case of changes as listed in Annex II of said regulations. Such applications were defined as extensions to the original MA with the same name. Yet the processing of such procedures lay outside the scope of the regulations.

For these newly named extensions, several rearrangements were also made, of which the most notable was that changes to or the addition of indications in a different therapeutic area were now classified as Type II by default.

The main features of the two types of variations are summarised in the following table:

	Type I		**Type II**	**Extension**
	Type IA	Type IB		
Approval	Acknowledgement of validity	implicit	explicit	MA
Time frame	14 days	30 days	60 days	210 days
Classification given in	Annex I	Annex I	-	Annex II

Table 3: Main features of the types of variations as introduced by Regulations 1084/2003/EC and 1085/2003/EC

[viii] Article 1(2) of Regulations (EC) No 541/95 and 542/95

[ix] Only those sections regarding indications, posology, contraindications, warnings, target species and withdrawal periods.

The next review of the legislation on performing variations on the European level was published with Regulation (EC) No 1234/2008[14] on December 12th, 2008 entering into force on January 1st, 2010.

This marked a departure from the former approach when separate regulations were issued for the different European procedures. For the first time, one regulation covered variation procedures performed in all European procedures such as CPs, MRPs and the DCPs[x].
As stated in the preamble of the regulation, the legislative update concerned an adjustment and improvement of the procedures in place while maintaining the general principles already established with earlier legislation. The scope of the Variation Regulation excludes purely national MAs implicitly and *homeopathic and traditional herbal medicinal products which have not been granted a marketing authorisation but are subject to a simplified registration procedure* explicitly.

One important change was the shift from "Type II by default" to "Type IB by default". Previously, if the change had not been listed in Annex I of Regulations 1084/2003/EC and 1085/2003/EC it was to be automatically classified in the category for major variations. This had the effect, that variations which were minor in nature but unforeseen at the time of drafting of the legislation had to follow the long timetable. This aspect was found to be quite burdensome for both applicants and authorities.

Furthermore, it was the explicit goal of the review to free up capacities especially on the side of the authorities. This was achieved by the introduction of the Type IA_{IN} category alongside with the annual reporting of minor Type IA variations. In an annual report, the notification of defined minor changes could be gathered and brought to the attention of the competent authorities within 12 months of their implementation. Since there are certain minor notifications that need to be submitted without delay such as a change in the name of the MAH, the complementing category of Type IA_{IN} was introduced. Yet, the change submitted in this category may also be implemented without awaiting approval. This proved to be a reversal of the former "tell and do" procedure to a "do and tell" approach.

With the previous legislations it had become apparent that the categorisation of the variations within the regulations was rather inflexible with respect to necessary updates. Therefore, with Regulation 1234/2008/EC the classification as formerly included in Annex I was removed to a separate document of legislative non-binding character, the 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[15] (Classification Guideline).
Other new concepts were the grouping of changes pursuant Article 7(2)(b) in the cases laid out in Annex III to the regulation or worksharing in accordance with Article 20. In a worksharing procedure the same change concerning more than one MA of the same MAH can be submitted.

As to the changes requiring the submission of an extension application, the categories remained unchanged, but were moved from Annex II to the new Annex I.

[x] Introduced with Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Article 28 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

A synopsis of the evolution of the variation system on the European level is given below.

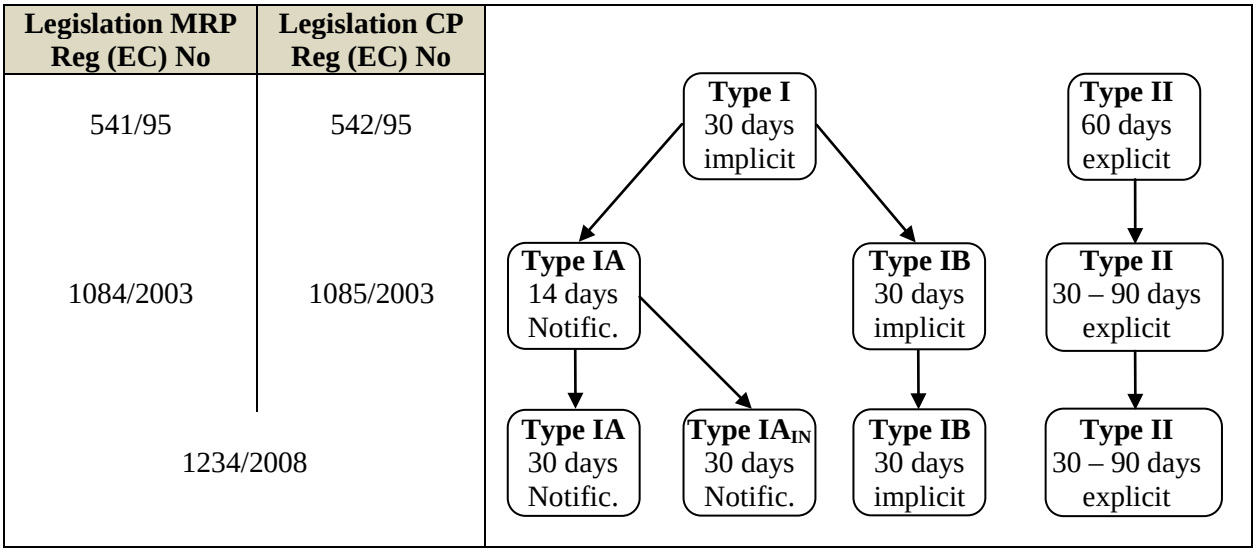

Figure 1: Development of the different types of variation categories

2.3 INTRODUCING DIRECTIVE 2009/53/EC AND THE UNIFICATION OF THE SYSTEMS TO IMPLEMENTING CHANGES

Up to this point, the conduct of variations in national and European procedures was kept separate with European legislation not addressing purely national procedures. This was regarded to be in blatant contrast to the harmonised provisions regulating the initial granting of MAs[16]. Hence, the effort was made to extend the European rules to national procedures also. This effort took the form of Directive 2009/53/EC[17] as published on June 30th, 2009.

With said Directive, both Directives 2001/82/EC and 2001/83/EC were amended as such empowering the EC to adopt an implementation regulation for the examination of variations of MAs granted in accordance with these Directives[xi]. The implementing regulation referred to in the amended Directives is Regulation 1234/2008/EC.

In contrast to regulations which are by definition directed towards every single citizen in the EU, directives address the Member States. Whereas the former legislative texts are to be applied directly, the provisions of directives need to be transposed into national law. For Directive 2009/53/EC, the implementation date for the changes was set to January 20th, 2011. A reference to the Directive 2009/53/EC was to be included in the national legal texts.

In the end, all the separate systems to performing changes to national MAs in the Member States are going to be supplanted with the variations system that is already in place for European procedures.

[xi] Article 27b into Directive 2001/82/EC and Article 23b into Directive 2001/83/EC

3 ISSUES UNDER EXAMINATION

The two systems for implementing changes for both national MAs in Germany and those belonging to a European procedure co-evolved over a considerable period of time. With the pending implementation of the provisions of Directive 2009/53/EC, the adaption of the variation system for national MAs in Germany is imminent.

Having introduced these two systems to handling change applications for MAs, a detailed comparison of the national and the European model is to be performed and their distinctive features to be carved out. With the insights gained, relative advantages and disadvantages of the two systems are to be identified and discussed.

Following this assessment, the wording and content of Directive 2009/53/EC as well as consequential changes to other legislative texts is to be examined. On the basis of this groundwork, an outlook on the national transposition efforts and pending revision of Section 29 of the German Drug Law is to be given.

Note:
In this work, the main focus is placed on human medicinal products for which the BfArM acts as the competent authority.

4 RESULTS

As given in the introduction, the concepts for performing changes to existing MAs on both the national level in Germany and on the European level developed in parallel for more than 15 years. Whereas the national system had been established in its general form quite early, the European model kept undergoing rather extensive changes with each consecutive revision. The latest general overhaul was implemented with the coming into force of the Variation Regulation 1234/2008/EC.

A superficial glance reveals extensive similarities. In both systems, it is differentiated between changes that may be implemented directly and those requiring prior approval from the competent authorities involved. These procedures mainly serve to implement changes to the MA in the course of the life cycle management.
Apart from these routine changes, there are such changes defined in both systems that may not be put into effect within the scope of those procedures. Rather, it is necessary to conduct extension applications, if applicable, or to submit a new MAA separate from the regular maintenance variations.

4.1 TAKING STOCK: COMPARISON OF THE PROCEDURES TO CONDUCT AND IMPLEMENT CHANGES

A closer look at both the national and European models for implementing changes to existing MAs reveals both similarities as well as striking differences.
With four different categories as currently in force, the European variation system features double the number of categories as compared to the national German model[xii].
This raises the question whether there are identical categories, close matches or different procedures altogether. For the purpose of assessment, the categories are to be aligned and compared in the following paragraphs.

Irrespective of the type of the change, the competent federal authority is to be notified without delay of the change to be introduced pursuant to section 29(1) AMG.
Furthermore, any change as covered by this section of the national drug law may be implemented following submission without awaiting approval. With these requirements, an almost identical procedure and the closest equivalent on the European level consequently is the Type IA_{IN} category of variations.

At the same time, it has to be stressed that the procedures may not be considered identical due to a subtle difference in the time point of implementation of the proposed change. As is the case for any Type IA variation, implementation may precede submission. For national MAs, changes may in any case only be implemented post-submisson, though. Also, for Type IA_{IN} procedures, a time line of 30 days is laid down in Article 8(2) of Regulation 1234/2008/EC whereas no time line is given for these changes on the national level. Nevertheless, since the changes may be implemented in both cases without awaiting approval, this aspect is of no further consequence.

[xii] Not counting changes necessitating the submission of a new MAA/ extension application

With this, a striking resemblance could be identified on the side of the variation categories for the first category of changes. When comparing the changes requiring prior approval as listed in Section 29(2a) of the AMG, the differences to the variation categories are more substantial and pronounced, though. On the one hand, the possibility for an implicit approval would make the Type IB category a close match. On the other hand, a shorter time table of only 30 days is followed in this type of variation. Consequently, the long time line of 3 months on the national level more closely matches the Type II category of variations. As a result, for changes requiring prior approval on the national level, no analogous variation type is identified. Since elements from the Type IB as well as Type II variations are included, the category may be considered a hybrid of the two.

Having paired up the two categories for performing national changes, it becomes evident that there is no direct counterpart to the Typ IA category in the AMG. As layed out before, changes are to be submitted without delay pursuant to Section 29(1). Consequently, accumulating minor changes of the Type IA category and submitting them with a delay of up to a maximum of 12 months is not covered by the current national drug law.

Introduced with Regulation 1234/2008/EC, the latter concept is a truly new and innovative regulatory tool on the European level. At the same time, these changes are by default limited to such changes that are considered not to impact safety, efficacy or quality of the medicinal product. Significant changes to the dossier are by definition ruled out and are covered by the higher variation categories. Therefore, this variation category includes basic administrative changes such as name changes for manufacturers or changes that serve to improve the control over a production process e.g. by introducing additional in-process testing.

Comparison of categories of changes for national MAs	**European procedures**
-	Type IA
Changes acc. to Section 29(1)	Type IA_{IN}
Changes acc. to Section 29(2a)	Type IB
	Type II

Table 4: Comparison of categories of changes for national MAs and European procedures

4.1.1 User-Friendliness of the Procedures to Implement Changes

Apart from the lower number in categories, another characteristic of the current national system to performing changes is that only the minority of changes requires prior approval by the competent federal authority.

In accordance with Section 29(2a) of the AMG, the number of changes requiring pre-approval is limited to a short, definitive list of 17 potential changes in this category. These changes mainly concern clinical issues with only a minority of 8 changes touching on manufacturing:

- [changes] *in the active substances, excluding the medically active constituents,*
- [changes] into *a pharmaceutical form which is comparable with the one authorised for marketing,*

- *treatment with ionizing radiation,*
- *manufacturing and test procedures or the indication of longer shelf-life for sera, vaccines, preparations derived from blood, allergens, test sera and test antigens as well as any change in manufacturing procedures using genetic engineering technology,*
- [changes] *in the package size.*

Explicitly, only the manufacture of special medicinal products is mentioned. This means that changes for the majority of authorised medicinal products containing chemical drug substances are not touched by these provisions. Any change to their manufacture may be introduced without requiring the competent federal authority´s approval. This is of a great advantage for the MAH. For instance, the implementation of the change immediately after receipt makes it possible that finished product produced for the application of an increase in batch size might be sold with sufficient shelf-life period left. The release lies in the responsibility of PE.

It may appear that there is a lack of supervision on the part of the competent authorities and a high degree of faith in the continued compliance with all the relevant guidelines and provisions on the side of the applicant. But this is not the case since the duty to supervise manufacturers as well as marketing authorisation holders is divvied up and delegated to the supervisory bodies of the federal states. Pursuant to Section 69(1) AMG, measures such as the prohibition of marketing or withdrawal from the market may be taken in case of non-compliance with relevant provisions. The grounds for these measures as given in this section are i.a. *that the medicinal product or the active substance has not been manufactured according to the acknowledged pharmaceutical principles or does not possess the appropriate quality in keeping with recognised pharmaceutical principles*[xiii].

This sharing and delegation of responsibilities regarding supervision of the PEs from the higher federal authorities may be a uniquely German feature. But this decentralisation serves an important purpose. In case a change does not require prior approval by the competent federal authority there is no basis foreseen in the regulatory framework of the AMG to allow for a rejection of the submitted change. This may only be issued in case of changes falling under Section 29(2a) AMG. Since the compliance with other provisions such as GMP for instance has to be ensured, this worksharing amongst the involved authorities serves as a fail safe mechanism to ensure the continued good quality of the medicinal products.

Overall, changes covered by Section 29(1) of the AMG mainly concern maintenance changes performed quite regularly in the course of the life cycle of a medicinal product. In contrast, the changes listed in Section 29(2a), such as the restriction of contra-indications or change into a comparable pharmaceutical form for instance, are not as commonplace and tend to occur rarely for a MA. With this, it becomes evident that the vast majority of changes submitted for national MAs in Germany may be implemented following receipt of the submission by the competent authority.

This is in stark contrast to classifying variations on the European level. For MAs falling under the scope of Regulation 1234/2008/EC, the foreseen changes are contained in the current Classification Guideline. Included therein is an extensive and highly detailed listing serving to assign possible changes to different variation categories.

[xiii] Section 69(1), number 2 AMG

Of the total of 273 variations explicitly listed in the guidance, 87 Type II and 60 Type IB variations are included. Put differently, more than half of the variations listed in the cited guidance require prior approval from either the RMS or the Agency.

Apart from the Type IB and II variations, a total of 83 Type IA and 43 Type IA_{IN} variations are included in the guideline. Yet, in case the conditions as listed in the guidance can not be fulfilled, the change is to be classified as a Type IB variation by default[xiv]. This serves to further reduce the number of occasions when a change may be implemented directly without waiting for approval – explicit or otherwise.

As given in Article 3(3) of Regulation 1234/2008/EC, a variation may even be re-classified by the competent authorities involved in case it is judged *that the variation may have a significant impact on the quality, safety or efficacy of the medicinal product concerned.* By definition, this change in category may affect only Type IB and not Type IA variations[xv]. But for the former category of variations, a change in classifcation leads to a decrease in planning reliability and significantly longer processing times until possible implementation of the change by the applicant. With these measures as described, there is a significant shift towards variations requiring prior approval on the European level.

When drafting the legislation, it was understood that including the definitions for classifying and conditions to performing variations in the Regulation itself made for significant inflexibility. Any update required to go through a lengthy legislative procedure. Hence it is to be considered a significant progress to include the classifications for the variations in a separate guidance document. The newly agreed guidance may be updated and adjusted more quickly.

But even so, a review is slated for the Variation Regulation as early as from January 1st, 2012 in order to take into account and adjust to recent developments[xvi]. Thus, the pace is set for the next revision of the legislation. It appears reasonable to expect to take less time to come into force than the more than 8 years between the current legislation on variations and that formerly in force.

In contrast to the European level, no requirement or date for compulsory review was set for the national legislation. Also, as had been the case on the European level before coming into force of the Variation Regulation, all the changes are classified and contained within Section 29 of the AMG. Consequently, there is no equivalent on the national level to the European Classification Guideline. A guidance document as published by the BfArM merely lists possible changes along with codes to be given on the application form to allow for a more efficient processing by the authority. Yet, all the listed change types are stringently classified in accordance with those defined in Section 29 of the AMG. Also, the current

[xiv] For simplification reasons, the classification of previously unforeseen changes employing the procedure according to Article 5 of Regulation 1234/2008/EC is not presented.

[xv] Article 2(2) of Regulation 1234/2008/EC: *Minor variation of type IA' means a variation which has only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned.*

[xvi] Article 26 of Regulation 1234/2008/EC: *By two years from the date referred to in the second subparagraph of Article 28, the Commission services shall assess the application of this Regulation as regards the classification of variations, with a view to proposing any necessary amendments to adapt Annexes I, II and V to take account of scientific and technical progress.*

legislation in Germany leaves no loop holes for reclassification of the changes as does the Variation Regulation.

Still, the national system allows for greater flexibility in comparison to the European one. In the light of the statements and conclusions made before this may appear surprising and the opposite might be expected. This is in great part to be attributed to the lesser degree of detail in the national German legislation.

This conclusion holds true even though the current variation system after entering into force of Regulation 1234/2008/EC has to be considered as a major progress in that the former "Type II by default" approach was abandoned in favour of "Type IB by default". Also, there is an increased flexibility of the variation system with the introduction of the procedure according to Article 5 of the Variation Regulation. With this procedure, unforeseen changes may be bindingly assigned a variation category.

Following the submission of the request for categorisation to either CMDh, CMDv or the Agency, a concerted recommendation is to be delivered within 45 days following receipt. In practice, the period required for receiving a joint recommendation from the coordination groups and the Agency is longer than that. In order to be able to discuss the requests at their respective meetings, recommended submission dates are given the applicant has to abide. In that, the start of the assessment following receipt can be delayed by up to a month following submission[18]. In case a request is to be submitted for a centrally authorised product, the Agency is to be informed of the intent of submission beforehand[19], thereby extending the required time even more.

Hence, this additional procedure according to Article 5 of the Variation Regulation requires a considerable amount of advance planning on behalf of the MAH. Only after the recommendation is made, the variation as intended may be submitted in the assigned variation category.

Nevertheless, the possible benefit for a classification in the Type IA category rather than "Type IB by default" makes for an incentive to seek this binding clarification. In the past, any unforeseen change was treated with in the highest variation category with no possibility for assigning a different classification. Hence, this new procedure serves to render the variations system more flexible by being able to account for changes that had not been anticipated at the time of drafting of the Classification Guideline.

Still, even with these leaps forward, the very lean national system in Germany outperforms the European one. Apart from not allowing re-classification of the category of changes, the vast majority of changes requires no approval prior to implementation by the applicant. The German system may hence be approximated by "Type IA_{IN} by default" as opposed to the European "Type IB by default". With this, even if the regulatory playing field shifts and unforeseen changes present themselves, they are still to be included in the lowest category of changes.

As a consequence, the national system makes for faster implementation, higher predictability and manageability of time lines on the side of the applicant.

4.1.2 Grouping of Variations

The flexibility of the national system is further illustrated by the concept of the grouping of variations. Whereas the grouping is a novelty and an improvement introduced with the Variation Regulation on the European level, it is a concept practised for changes to national MAs in Germany for a long time now. In European procedures only certain combinations regarding related changes as detailed in Annex III to the Regulation are regarded as acceptable. Also, the CMDh publishes updates at regular intervals on acceptable groupings[20]. For instance, the change to specification limits as well as to the corresponding methods may be submitted as a grouped variation. Yet altering another method not affected by the specification update is treated as a mere temporal coincidence and not a consequential change. Hence, is does not constitute an acceptable grouping and would lead to a rejection of the grouped application.

In case no information on the intended grouping is published yet, it is expected of the MAH to contact the RMS in charge or the Agency prior to the submission of the changes. As opposed to the procedure according to Article 5 of the Variation Regulation, no special procedure leading to a harmonised decision or time line is laid down. This has the effect that from different authorities different interpretations and opinions may be obtained. As a result there is some degree of uncertainty for the applicant. But this may be overcome with time as both sides gain more experience in preparing and handling such procedures.

As opposed to this approach, there is effectively no limit for national procedures to what changes may be submitted simultaneously and listed on a single application form. This means that, for example, changes concerning the quality of the drug product may be grouped with an update of the Detailed Description of the Pharmacovigilance System (DDPS) as well as an extension of the side effect section in the SmPC and PIL. Consequently, not only consequential changes but all alterations to MAs that present themselves at any one time and are not necessarily interrelated may be applied for simultaneously.

Hence, what requires meticulous scouring for information on authorities´ homepages, interpretation of guidelines and liaison with authorities in case the intended grouping is not listed for European procedures, may be submitted without any additional considerations for national MAs. With this, the current system to implementing changes for national MAs in Germany is one of the most applicant friendly systems conceivable.

In addition to the fact that there are no restrictions to the grouping of changes on the national level, MAHs are steered towards the grouping of changes by the effective means of holding out the carrot of a fee reduction. For medicinal products falling into the responsibility of the BfArM or the BVL, every additional change submitted within the scope of one application, the applicant is required to pay only half rates on top of the full rate for the most expensive change. Interestingly, this sort of incentive is not given for European variations by the Fees Ordinance[21] of the BfArM or the Statutory Cost Regulations for Official Duties for medicinal products being supervised by the Paul-Ehrlich-Institut (PEI)[22]. For each change the full fee has to be paid with no reduced rates available.

With regards to the procedures to be followed, grouped applications are handled according to the highest category included in the application for both national and European procedures. As detailed above, only the comparatively small number of 17 listed changes entails the

requirement to wait for an implicit approval following submission of the change. Keeping this fact in mind, the probability that the implementation of a group of changes requires pre-approval is comparatively low for national MAs in Germany. This is in contrast with the European variations system where the odds of including a variation requiring approval are high to begin with. In a grouping scenario the odds to be falling into a pre-approval category are increased even further.

Also, while Type IB variations offer the possibility for an implicit approval after 30 days, this scenario is often hampered in the experience of the applicant and delays at various stages of the procedure are commonplace. Although Type IB and II variations offer seemingly rigid time lines pursuant Articles 9 and 10 of Regulation 1234/2008/EC, there are ample possibilities that the boundaries are stretched. Mainly, this concerns the delay of the start due to validation issues as well as largely unpredictable clock stop periods for both the applicant´s and authorities´ side.

Insofar, the national system again is leaner in this administrative aspect. For one, there is no formal 14-day validation which is routinely exceeded in the experience of the applicant. For national MAs, the clock is started for changes requiring pre-approval on the day the documentation including the originally signed application form is physically received by the competent federal authority.
This places the pressure to meet the 3-month deadline squarely on the shoulder of the competent authority thereby favouring the applicant. Combined with an implicit approval once time runs out, the required resources to assess the change in the required time need to be allocated efficiently on the authorities´ side.

Unfortunately, apart from the described advantages of the national system, there is also an outdated aspect that does not make for efficient processing of applications. As such, in contrast to European procedures, a list of questions and the possibility for a clock stop to prepare and submit additional documentation is not built into the national procedure. This entails the lack of a possibility for interaction between the applicant and the authority in due course. In case the submission does not fulfil the necessary requirements for approval, the only possible consequence is an outright rejection on the grounds of Section 25(2) AMG. Among the listed reasons for rejection are incomplete documentation, insufficient testing, inappropriate quality or lacking therapeutic efficacy.
The deficient aspects of the submission may be included in the grounds for the rejection. These have to be considered and improved upon by the applicant when resubmitting the change.

Yet, changes requiring pre-approval pursuant to section 29(2a) of the AMG tend to be changes which are *per se* complex in nature, such as the addition of a therapeutic indication in the same therapeutic area for instance. Such a change application is accompanied by large quantities of detailed documentation taking into consideration all the current legislation and guidance issued. Due to the lack of dialogue between the competent authority and the applicant during the procedure, the threat of a rejection looms larger for those national changes than for a variation.

In the worst case scenario of a rejection close to the 3 month deadline, the time loss relative to a variation for the applicant is considerable. Instead of working from the common base of the initially deficient variation application within a response document the whole procedure is

restarted. With the resubmission of the application, the complete assessment of the documentation tends to start anew. This might also entail that the application is handled by a different assessor. On the European level the procedure is followed through in the most cases with one assessor assigned to it. *A priori* it should be easier to assure consistency in the decisions in the latter scenario. This is true only assuming no additional internal measures are taken by the national competent authorities to avert this.

Apart from the general differences in the systems to changing existing MAs, the classification of the changes is not the same, as exemplified above. This is to be summarised for those changes requiring prior approval pursuant to Section 29(2a) AMG. In the following table, the changes listed therein are aligned with their closest match in the European system.

Change in accordance with Section 29(2a):	**Variation Type**	**Classification**
1. dosage	II	C.I.4
nature of the administration	II	C.I.4
duration of the administration	II	C.I.4
therapeutic indications	IB/ II	C.I.6
limitation of the contra-indications	IB / II	C.I.3
limitation of side-effects	II	C.I.4
limitation of interactions with other substances		
2. active substances, excluding the medically active constituents	IB / II	B.II.a.3.b
3. pharmaceutical form which is comparable with the one authorised for marketing	EA	-
3a treatment with ionizing radiation,	IB by default	Not foreseen
4. manufacturing for sera, vaccines, preparations derived from blood, allergens, test sera and test antigens change in manufacturing procedures using genetic engineering technology	II IB/ II IB/ II	B.II.b.3 B.II.b.4 B.II.b.5
test procedures for sera, vaccines, preparations derived from blood, allergens, test sera and test antigens	IB/ II	B.II.d.2
longer shelf-life for sera, vaccines, preparations derived from blood, allergens, test sera and test antigens	IA_{IN}/ IB/ II	B.II.f.1
5. pack size	IA/ IA_{IN}/ IB/ II	B.II.e.5
6. withdrawal period due to change in a maximum residue limit	II	C.II.3
withdrawal period if the withdrawal period-determining component of a fixed combination is no longer contained	II	C.II.3

Table 5: Comparison of national changes requiring prior approval with their respective classification in accordance with the Classification Guideline

Interestingly, on the European level an update of the safety relevant information is to be submitted as a variation requiring prior approval under all circumstances. In the national system in Germany, though, approval from the competent authority is only to be awaited in case of limitations to contra-indications, side effects and interactions with other substances. This allows for a quick implementation of new signals obtained through pharmacovigilance efforts.

For European procedures, such a fast implementation is only foreseen in case of an *event of risk to public or animal health*. Under such circumstances a USR may be performed in accordance with Article 9 of the Variation Regulation. Yet, the USR is seen as a measure of last resort serving to avert looming life-threatening situations. Hence, the USR is employed quite rarely. Consequently, an update of the safety information is performed mainly by way of variation requiring prior approval. This in turn leads to the conclusion that for national MAs updates of the SmPC and PIL due to new safety information may be made available much faster to health care professionals as well as patients. Thereby, the cause of improving the safety of the products is furthered.

Yet the national system is not so much to be praised when it comes to implementing interrelated changes such as the update of the Core Safety Profile (CSP) following a PSUR Work Sharing Procedure. As the outcome of the Work Sharing Procedure (WSP), the harmonised text of the safety relevant sections 4.3 to 4.9 of the SmPC is published. Especially the first time the WSP is performed, the text of the SmPC usually requires broad revisions spanning all the mentioned sections. In the variation system, a single Type IB variation may be submitted to adapt the SmPC to the CSP. On the national level, single changes for each of the sections affected by changes need to be submitted. Apart from the added costs, there is a high probability that a fraction of the submitted changes is automatically to be classified as requiring prior approval, e.g. in case a limitation of side-effects is involved.

The approach to strictly abide by the letter of the law is consequent by the competent national authorities, of course. In this instance, though, the changes to be implemented were already discussed with and assessed by another or even the same competent authority. It would therefore seem appropriate to provide the possibility to perform a literal transposition of the outcome in the course of a “do and tell” procedure. For European procedures the classification as a Type IB procedure appears justified. Since national translations are involved, the competent authorities are to be given time for the assessment and the possibility to raise issues. A list of questions is not foreseen within the scope of a Type IA_{IN} procedure.

Nevertheless, Section 29(2a) does not grant the necessary leeway and the interpretation from the authorities´ side is strict and literal. A further example to underscore this is the BfArM´s current administrative practice with regards to updates to the SmPC. In case a change is intended in sections 4.1 (Therapeutic indications) and 4.2 (Posology and method of administration) of the SmPC, it is automatically to be classified as requiring prior approval by the competent authority. This classification is irrespective of the nature of the change. The addition of an indication is treated the same way as a formal update of the texts in the mentioned sections[23]. Although this may not be regarded as a practical approach by the applicant, it is accepted as consequent and in line with the AMG.

Apart from the exception of the worst case scenario of a late rejection of changes requiring prior approval, the national system in Germany allows for reliable planning on the side of the

applicant. Either the change may be implemented following the receipt of the documentation by the competent national authority or a period of 3 months has to be waited. In most cases, the time to implementation of the proposed change is faster than compared to the variations system.

The distinct time lines are in contrast to the somewhat unpredictable ones inherent to the variations system for variations requiring approval prior to implementation. Also, the simplicity of grouping and submitting simultaneously any change irrespective of interrelatedness distinguishes the current national system from the European one. Taken together, in the majority of cases, the national system to implementing changes to existing national MAs is quicker, more efficient and more predictable with respect to the time lines than the European variations system as laid down in Regulation 1234/2008/EC.

4.2 CHANGES NECESSITATING THE SUBMISSION OF A NEW MAA

Apart from the changes that may be performed several times in the life cycle of a MA, there are those that are regarded to be so substantial that a full assessment by the competent authorities is required.
For national MAs this leads to the requirement of the submission of an application for a new marketing authorisation pursuant to section 29(3) of the AMG. In the strict sense, this may not be interpreted as a variation procedure on the national level. But since the cause of the application is a change to an existing authorisation, it is comprehensible to include those changes in the same section of the AMG.

On the European level, a distinction is made between a new application and an extension of the existing, initial MA. All the changes leading to the requirement to perform an extension application are given in Annex I of the Variation Regulation. It is made clear that such applications *fall outside the definition of a variation to a marketing authorisation*[24]. In contrast to regular maintenance variations the legislation does not allow for any exceptions or any possibility for a re-classification into another category. As given in Article 19 of the Variation Regulation, *an application for an extension of a marketing authorisation shall be evaluated in accordance with the same procedure as for the initial marketing authorisation to which it relates. An extension shall either be granted a marketing authorisation in accordance with the same procedure as for the granting of the initial marketing authorisation to which it relates or be included in that marketing authorisation.*

In effect, on both the national and European level, particular changes require the submission of a new MAA in line with the procedure that was initially followed. But in contrast to MAAs to be submitted nationally, extension applications on the European level are inadvertently linked in a global MA pursuant to Article 6 of Directive 2001/83/EC. The same invented name as in the initial procedure is to be used. Furthermore, the applications may also share the same procedure[xvii] or even marketing authorisation number[xviii]. For national MAs the inclusion within a global MA pursuant to Article 25(9) AMG is only permissible unless it is expressly and actively applied for at the time of submission. Otherwise, quintessentially independent MAs are granted.

[xvii] To be distinguished by the sequential speciality number for each presentation (pharmaceutical form and/ or strength)

[xviii] Depending on the statutes in the respective Member State

Also, for European procedures, extension applications require the same legal basis as the initial application for marketing authorisation[25]. In case these prerequisites can not be fulfilled, an independent application for a new MA has to be submitted. For national authorisations in Germany, no mention of such a pre-condition is made in the current drug law. This is of no consequence, though, as the concept of an extension application does not exist on the national level and hence such a pre-condition is not required.

Yet, even when the intended change necessitates an extension application, its submission is not compulsory. In its stead, an independent application for marketing authorisation may be submitted using a different invented name or SmPC[24]. Still, the concept of a global MA is automatically applied in this case also.

Apart from the identical name, possibly a fee reduction and the inclusion into the global MA, the extension application very much resembles the procedure to aquire a new MA. For extension applications there is no separate procedure to be followed which might have a more compact time line allowing for acceleration of the authorisation process.
Even without a separate procedure, performing a European procedure is currently to be preferred given that it fits the regulatory strategy of the applicant. At least in case the medicinal product to be applied for falls under the competence of the BfArM, national procedures tend to take longer to complete than the stipulated 210 days[26].

As observed in the previous section on maintenance variations, there are significant differences in the listed changes leading to the submission of new MAA. Only two requirements are found to be rather similar:

For one, changes to the active substance of the drug product range first on both lists. But whereas in Section 29(3), number 1 AMG it is merely stated that a *change in the composition of the active substances either in type or quantity* leads to the requirement to submit a new MAA, a list of 6 subnumbers is included in Annex I, number 1 of the Variation Regulation. Also, the aforementioned distinction between the national and the European system becomes evident in this context. Pursuant to Annex I of the Variation Regulation only such changes to the active substances are allowed to be classified as an extension to an existing MA in case *the efficacy/ safety characteristics are not significantly different.* Hence, any change to the active substance that requires it to be defined as a new active substance [xix] is excluded from the possibility of submitting an extension application. Instead, a separate MAA has to be submitted.

The second similarity lies in the change of the pharmaceutical form. For European procedures, the pharmaceutical form may be changed or an additional one included. The latter possibility is not provided for on the national level. By default, separate MAs for different pharmaceutical forms are granted.

Apart from this similarity, there are also differences as underlined by the relevant guidance[27]. Therein, the pharmaceutical form is as defined by the Standard Terms of the EDQM. It is

[xix] Notice to Applicants, Volume 2A, Chapter 1, Annex III

furthermore stated that *a change or addition of pharmaceutical form results in an Extension Application except in case of a deletion of the solvent* [xx].

In contrast, the requirement to apply for a new MAA is not as strict on the national level. In section 29(3), number 2, an exception is made for pharmaceutical forms comparable to the currently authorised one resulting in the exemption from the requirement to submit a new MAA. Pursuant to Section 29(2a), number 3, the submission of a change requiring pre-approval is sufficient in this instance. The result of such an application may only be a change but not an addition of a pharmaceutical form on the national level.

Additionally, the definition of a comparable pharmaceutical form as published is more far-reaching on the national level and includes the following pharmaceutical forms as summarised under a single indent[28]:

- *all oral immediate release,*
- *all oral delayed release,*
- *buccal and sublingual,*
- *rectal,*
- *vaginal,*
- [pharmaceutical forms for] *topical application (depending on the composition of the active substance free base, the resorption conditions and place of application)*
- *pharmaceutical forms intended for inhalation,*
- *transdermal systems,*
- *immediate release solutions for injection (depending on the route of administration) ,*
- *delayed release solutions for injection (depending on the route of administration),*
- *solutions for infusion.*

Yet, for the listed pharmaceutical forms, comparability may not automatically be inferred, but the *release, bioavailability as well as the bioavailability at the target organ* need to be taken into consideration also.

These requirements were further elaborated in a separate Announcement[29]. Apart from the unchanged pharmacokinetic parameters it is given that the *route of application, profile of resorption and the galenic vehicle and the resulting in vitro release* are to be taken into consideration. The conclusion is drawn that a comparable pharmaceutical form is given if the *the aggregate state, route and place of application are identical and that the release and bioavailability of the active substance are approximately the same.*

Although not expressly listed, pharmaceutical forms that require conversion prior to application to the patient are also included in this definition. For instance, this concerns powders for solution for injection and/ or infusion and concentrates for solutions for injection and/ or infusion. The appraisal is comprehensible as there is no difference in the medicinal product that is administered to the patient. In either case a solution is parenterally injected or infused. The only difference consists of an additional preparation step (reconstitution) prior to dilution to be performed for the powder.

[xx] The change aspects leading to the requirement to submit an extension application were not altered with Regulation 1234/2008/EC. Hence, the guidance document remains relevant. It requires updating, though, to consider the changes in the categorisation of the variations.

Compared to the very restrictive definition of the pharmaceutical form on the European level, these national provisions allow for a regulatory easier and swifter implementation.

Yet apart from the unambigous example as given above, the MAH is always required to prove unchanged pharmacokinetic properties in order to claim a comparable pharmaceutical form. In this, the national requirements very much resemble those in Annex I, number 1, sub-numbers 2a and 2b of the Variation Regulation. It is stated therein that a change of bioavailability and of pharmacokinetics e.g. through a change in the release rate as a result of changes to pharmaceutical form i.a. leads to the requirement of the submission of an extension application.

Apart from these change aspects, the requirements as to when to submit a new MAA or extension application to the competent authorities differ widely. For various other categories, no consistency between national and European requirements can be established. The intended change may be submitted as a variation in European procedures but as a new application for national MAs or vice versa.

For example, a new therapeutic indication may be added within the scope of a Type II variation on the European level in any instance. The variation category to be chosen may even be as low as Type IA_{IN} in case of a referral procedure in accordance with Articles 30 or 31 of Directive 2001/83/EC or Articles 34 or 35 of Directive 2001/82/EC.

For national MAs by contrast, a distinction is made whether the indication applied for lies within or outside the currently approved area of therapy. The dividing line is drawn on the 3rd level of the ATC code[29]. As belonging to the same therapeutic area those indications are grouped that are part of the same therapeutic / pharmacological subgroup. For changes within these bounds of the ATC code, an application requiring prior approval pursuant to Article 29(2a) is to be submitted. In case the intended indication lies outside the 3rd level of the ATC code, a new MAA is required. In any case, the change is weighed to be more substantial on the national level as judged by the differences in classification.

Accordingly, the much longer time frame of 210 days for granting a new MAA is set in accordance with the relevant legislation[xxi] in contrast to the 90 days for a Type II variation. In consequence, the medicinal product may be made available in the new indication significantly later in the national setting.

Also, the requirement to submit a new MAA entails that the existing MA remains valid and an additional MA is granted in case of an acceptable submission. This duplication of MAs on the grounds of indication e.g. leads to an increase in both cost and effort throughout the life cycle of the product. Economic considerations on the side of the applicant may lead to the withdrawal of the initial MA thereby reducing the number of alternatives on the market.

For European procedures there are no restrictions to altering or adding to the initially approved indications within the scope of mainly Type II variations. For instance, methotrexate containing tablets can be approved on the European level in a single MA for antirheumatic, antipsoriatic and cytostatic indications with the corresponding

[xxi] Article 21(1) of Directive 2001/82/EC as amended and Article 17(1) of Directive 2001/83/EC as amended

pharmacotherapeutic groups being “Other immunosuppressants” (ATC-code: L04AX03) and “Antimetabolites, folic acid and analogues” (ATC-code: L01BA01)[30] as opposed to two MAs on the national level. With this, the European model proves to be more flexible and quicker when implementing changes to indications.

This is also the case for changes to the manufacturing process. For national MAs, there is a requirement to submit a new MAA further to number 3a of Section 29(3) AMG in case genetic engineering is to be introduced. This is in marked contrast to MAs falling under the scope of Regulation 1234/2008/EC. In Annex I to said Regulation not even a single change to the manufacturing process is listed as requiring the submission of an extension application. Furthermore, no mention is made in the Classification Guideline for variations regarding genetic engineering. As given in the changes´ conditions section, restrictions on performing minor variations are only imposed on biological, immunological or herbal medicinal products.

As a counterexample with reversed roles, a change of the route of administration may be taken. On the European level an extension application needs to be filed with the competent authorities. For nationally approved medicinal products it is sufficient to submit a change requiring prior approval pursuant to Section 29(2a) of the AMG. Yet it appears that such changes occur seldomly and not isolated from other significant changes. It stands to reason that a change in pharmaceutical form is commonly interconnected with additional, concomitant alterations to the MA. For instance, the pharmaceutical form of a solution for injection may be used not only for intravenous but also for intravesical use.

With the change to the route of administration the indication in which the medicinal product is used will probably be altered in parallel. As given above, this may result in either a change requiring pre-approval or even the submission of a new MAA. Also, changing the route of administration may not be possible without further, consequential changes to the pharmaceutical form. The latter change requires the submission of a new MAA in case the new pharmaceutical form is not considered comparable to the currently approved one such as a tablet given orally to a dermal patch.
Therefore, the categorisation of concomitant changes may yet result in a classification of a change requiring the submission of a new MAA to the competent authorities.

Taken together, the changes that require the submission of a new MAA or an extension application are not harmonised on the national and the European levels. Rather, the majority of the listed changes leading to the submission of a new MAA may be submitted as a variation in a European procedure as given in the table below.

Change in accordance with Section 29(3):	Classification acc. Var. Reg.
1. change in the composition of the active substances either in type or quantity	Extension application
2. change in the pharmaceutical form unless a change pursuant to sub-section 2a number 3 is concerned	Extension application
3. extension of the therapeutic indications, in so far as this does not constitute a change pursuant to sub-section 2a number 1	Variation application
3a. introduction of manufacturing procedures using genetic engineering	Variation application
5. reduction of the withdrawal period, in so far as a change pursuant to sub-section 2a sentence 1 number 6 is not concerned	Variation application

Table 6: Comparison of national changes requiring the submission of a new MAA with their respective classification in accordance with the Variation Regulation

At the same time, the AMG allows for an exception when a change of the pharmaceutical form is applied for. The concept of a comparable pharmaceutical form is not established on the European level but rather reasonably defined and applied for national MAs.

4.3 CONSEQUENCES OF THE COMING INTO FORCE OF DIRECTIVE 2009/53/EC

In line with Article 1(3) of the Variation Regulation, the measures to alter MAs by way of variation apply only for national MAs granted via MRP/ DCP or for MAs granted following a CP. Marketing authorisations licensed in a single Member State currently lie outside the scope of the Variation Regulation, as do homeopathic and traditional herbal medicinal products subject to a simplified registration procedure.

In consequence, there is no possibility as of yet to include national MAs in the procedures described therein such as a worksharing procedure. All the life cycle management activities for these MAs need to be performed taking into consideration the separate laws of the single Member States.

This shortcoming of the Variation Regulation was readily identified. In order to achieve full harmonisation on the European level, two steps were required to be taken. For one, the separate provisions to implementing changes on the national level were to be brought in line with the variation system for European procedures. Secondly, the scope of the Variation Regulation needed to be extended to cover those MAs granted in single Member States also.

All the national drug laws in the Member States are required to comply with the overarching Community code relating to veterinary as well as human medicinal products, namely Directives 2001/82/EC and 2001/83/EC. Hence, the means to addressing these two objectives needed to take the form of amendments to both Directives to be appropriately transposed into national law by the Member States.

On June 18th, 2009, Directive 2009/53/EC was agreed upon as the result of the legislative co-decision process. The Directive amending Directives 2001/82/EC and 2001/83/EC entered into force 20 days following its publication on July 20th, 2009.

Through the amendments to both Directives, the European Commission was empowered to *adopt appropriate arrangements for the examination of variations to the terms of marketing authorisations granted in accordance with this Directive.* The arrangement referred to in the newly included Article 27b(1) of Directive 2001/82/EC and Article 23b(1) of Directive 2001/83/EC of course is the implementing Regulation 1234/2008/EC already in place. With this measure, preparations were made to mandatorily extend the variations system as established for European procedures to MAs granted in a single Member State.

Prior to the amendment by way of Directive 2009/53/EC, provisions almost identical in wording empowered the Commission to *adopt appropriate arrangements for the examination of variations to the terms of a marketing authorization* in consultation with the Agency[xxii]. Located in Chapter 4 of Title III of the two Directives, only the European procedures MRP and DCP were addressed, though. In turn with the inclusion of the new arrangements covering all types of MAs, the reference to the provisions formerly in place was consequently deleted[xxiii].

Also, the reference to the involvement of the Agency no longer requires mentioning in this context since a single, harmonised approach to conducting variations was implemented with the new Variation Regulation. Before, two separate Regulations had been in place laying down the requirements for MAs granted following MRPs and DCPs as well as those medicinal products approved by way of CP.

While the measures as described before in this section comprise the only amendments to Directive 2001/82/EC governing veterinary medicinal products, several additional measures were included in the new Article 23b of Directive 2001/83/EC for human medicinal products.

In subparagraph 3 of Article 23b, the EC is called upon to create the possibility to *submit a single application for one or more identical changes made to the terms of a number of marketing authorisations.* The procedures to perform grouping and in particular worksharing are already detailed in the Variation Regulation[xxiv]. Hence, the paragraph appears to be redundant. Yet, in Article 20 of the Variation Regulation it was foreseen that worksharing for Type IB and II variations be applicable only for such MAs that were granted by different Member States or through different procedures.

With the amendment to Directive 2001/83/EC, the EC is asked to extend the scope of this measure when reviewing the provisions as laid down in the Variation Regulation. For the future, the possibility is to be created to submit a number of changes within a single application for one or more MAs authorised in a single Member State[xxv]. Since only one competent authority is involved in this case, worksharing would not be possible under the

[xxii] Second and third subparagraphs of Article 39(1) of Directive 2001/82/EC and second and third subparagraphs of Article 35(1) of Directive 2001/83/EC

[xxiii] Articles 1(2) and 2(2) of Directive 2009/53/EC

[xxiv] Article 7 on grouping and Article 20 on the worksharing procedure of Regulation 1234/2008/EC,

[xxv] Article 23b(3) of Regulation 1234/2008/EC

current legislation. The measure thus serves to further harmonisation and is projected to reduce the administrative burden for both MAHs and competent authorities.

Curiously, this particular work assignment for the EC was incorporated into the legislation governing human medicinal products only. Since the rules to performing variations to MAs are contained in a single regulation for both human and veterinary medicinal products this measure is sufficient to cover both groups.

The EC took on the assignment as given in Directive 2009/53/EC and set to work to extend the scope of the Variation Regulation and include national MAs. On September 21st, 2011 a Public Consultation Paper for the Review of the Variation Regulation was published allowing a one-month period for contributions from stakeholders[31]. From the analysis of the submitted comments and proposals the further comitology process to amend the Variation Regulation is to commence.

In the legislative process of the drafting of Directive 2009/53/EC, the involved parties refrained from demanding additional measures for registered homeopathic medicines and traditional herbal medicines. The conclusion was drawn that excluding these special medicinal products *avoids complicating a registration procedure which was simpler in some Member States*[32]. As a result, these types of medicinal products will continue to lie outside the harmonised system to conducting variations.

With Article 23b(4) of the Directive, an exception to the applicability of the harmonised rules to perform variations is introduced. Member States are allowed to continue to apply national provisions for national MAs granted before January 1st, 1998. If this option was chosen, the EC was to be informed thereof in accordance with Article 23b(5) of the Directive. If not, the implementing regulation was to universally apply from January 20th, 2011.

The cut-off date of January 1st, 1998 coincides with the coming into force of Article 1(7) of Directive 93/39/EEC amending Directive 65/65/EEC. This date set the deadline for the requirement to perform a MRP in order to acquire additional MAs further to an already approved national licence. Hence, the date appears to be appropriate.

These separate national measures may not be applied indefinitely, though. In the same subparagraph, a limitation is included. In case further MAs are subsequently granted in other Member States, these diverging provisions are superseded. In their stead the variation system as described in the implementing regulation will need to be applied.

In accordance with Article 32(2) of Directive 2001/82/EC and Article 28(2) of Directive 2001/83/EC, any such additional MA may only be granted within the scope of a MRP. Hence, from the day of the granting of any additional MA, the complete procedure falls within the scope of the Variation Regulation. This is consequential and in line with the provisions already in place.

As a deadline to take the appropriate legislative measures to comply with the provisions of Directive 2009/53/EC, the Member States were given 18 months until January 20th, 2011[xxvi]. The Commission was to be appropriately informed of the national execution measures and

[xxvi] Article 3(1) of Directive 2009/53/EC

legal texts. From Germany´s side this took the form of a concordance table[33] which was provided in a timely fashion.

With this, a step towards harmonised rules to conducting variations for all medicinal products, irrespective of the initial authorisation procedure was taken.

4.4 FORESHADOWS OF THE VARIATIONS SYSTEM

Although the date of the transposition was set, the pace of the implementation of the provisions of Directive 2009/53/EC differed widely afterwards in the separate Member States.

In a considerable number of Member States the variation system was in place simultaneously for European procedures and purely national MAs when Regulation 1234/2008/EC entered into force on January 1st, 2010. An overview of these Member States is given in Table **7** below.

Implementation date for national MAs from	**Human medicinal products**[34]	**Veterinary medicinal products**[35]
January 1st, 2010	BE, CY, EE, EL, HU, IT, NL, SI, SK, UK	DE (PEI), FR, HU, LT, NL, NO, PL, PT, SI
January 1st, 2010 with different time lines	DK, ES, FI, IE, IS, LT, MT, NO, RO, SE	DK, FI, IE, IS, SE

Table 7: Status of implementation of Regulation 1234/2008/EC for national MAs on January 1st, 2010

Whatever the motives or legislative necessities of the other Member States at first glance it is quite interesting to notice that in Germany the PEI accepted variation applications for national MAs also from that early time point on. Both the BfArM and the BVL continued to process changes to purely national MAs in accordance to Section 29 of the AMG.

But those medicinal products for veterinary use, namely vaccines and immune sera, for which the PEI acts as the competent authority are not governed by the AMG. Instead these special medicinal products used in the context of animal diseases fall under the scope of the Veterinary Vaccines Act[xxvii].

In said Veterinary Vaccines Act, the European variation system was already taken into account when first coming into force on November 1st, 2006. In Section 29 relating to changes to the MA, a reference to the relevant articles of Regulation 1084/2003/EC was included at that time. This reference was updated to the respective passages of Regulation 1234/2008/EC when the revision of the Act was passed on September 29th, 2011.

Hence, the handling of variations for national MAs by the PEI is not remarkable. For the other medicinal products the legislative procedure to implement the provisions of Directive 2009/53/EC into the AMG was not publicly initiated on January 1st, 2010. Even 18 months

[xxvii] "Tierimpfstoffverordnung"

later, when the deadline for the transposition passed, a draft for public consultation was still outstanding.

For the PEI, the involvement in variation procedures including national MAs does not stop with this. In November and December 2011, the CMDv and CMDh stressed in their respective meeting reports that medicinal products authorised through national procedures remained to be excluded from worksharing procedures pending the amendment of the Variation Regulation[36,37]. Yet only three months later the CMDv announced that the PEI was requested to act as the designated reference authority in a so-called *informal worksharing procedure*[38]. The term was thus coined since the procedure included purely national MAs alongside MAs granted in European procedures.

Although not overly publicised, such procedures had already been allowed and performed before coming into force of the Variation Regulation. The motiviation behind implementing such an informal worksharing system had been the efficient management of available resources[xxviii].

Whereas the CMDv again published information about informal worksharing in March 2011, the CMDh kept reminding the MAHs that nationally authorised *medicinal products cannot be part of grouping and worksharing procedures until the Regulation is amended to include national products*[39]. Hence, the informal procedure remained restricted to veterinary medicinal products. It was employed on further occasions again involving the PEI[40]. In total, 19 informal worksharing procedures were accepted by the CMDv in 2010 and 22 such procedures greenlit up to November 2011[xxviii].

As stressed by the CMDv, the experience gained when conducting worksharing procedures including purely national MAs is likely to prove beneficial in the initiated extension of the scope of the Variation Regulation to purely national MAs[41].

Nationally, the PEI was at the forefront in gaining experience when combining national and European MAs in a single submission. But although its role was more prominent, the way to submit changes to MAs on the national level was altered for the BfArM as well.

From April 20th, 2007 updates to MAs could be submitted via the newly established portal to be accessed via the PharmNet.Bund.de website[42]. In its first installment, only those MAs for which the BfArM acts as the competent national authority could be addressed. In August 2010, the second expansion stage of the portal went into service. Among other upgrades, it was made possible to also conduct submissions for MAs handled by the PEI. More importantly, a feature was added to form groups of MAs for which any number of identical changes requiring the same documentation could be submitted[43]. When concluding the preparation of the electronic submission only a single application form is generated listing all MAs affected by the changes applied for.

This new feature was not overly touted as such, but in essence it marked the pragmatic start of worksharing for national MAs clad in the guise of an administrative simplification for online submissions only. In case the portal is not used in a change application, the policy to fill in

[xxviii] Personal communication with Dr. Esther Werner, PEI, Chair CMDv

one application form per MA was not updated alongside. Instead, *a separate application for each medicinal product changed* still needs to be submitted to the BfArM[44].

As becomes apparent, the variations system already exerted its influence in the conduct of national change procedures for existing MAs before it was legally implemented.

4.5 Reality Check: Publication of a First Draft of the Updated Section 29

The transposition of appropriate legislative measures in Germany appeared to be the source of intense consultations as can be interpreted from the long time coming. This was hardly surprising. Presently, there is a rather efficient system in place that is even recognised as such on the European level[45]. This proven and tested system is now on the verge of a significant revision. The question is whether there is a willingness to keep aspects of the current system within the constraints of the given legal framework. At least from the side of industry associations the wish to do so was expressed[46].

At present, the AMG does not distinguish between submitting change applications for human or veterinary medicinal products. This in turn leads to expect that following the transposition of Directive 2009/53/EC into national Drug Law the single, harmonised set of rules to conducting changes is maintained.

With this in mind, the inclusion of exceptions for the sizeable subcategory of human medicinal products authorised before January 1st, 1998 are unlikely. As given before, a corresponding provision to keep deviating provisions for a subset of MAs was not included in Directive 2001/82/EC concerning veterinary medicinal products. Hence, an exception would not concern such MAs. At the same time it is questionable if the two competent authorities involved would be motivated to make the distinction. Clearly, it would amount to additional administrative burden for the BfArM and PEI.

For one, a way to identify MAs eligible for a separate set of rules to conducting changes would need to be devised. In case a submission is made by hard copy, the current application forms of both BfArM and PEI do not require the date of the granting of the MA to be given. Yet this information is essential in order to be able to make the distinction which procedure to follow. But even the simple ticking of a box on the application form generates additional administrative effort. This would concern both the applicant when preparing the submission as well as the authorities in the course of validation.

For electronic submissions via the PharmNet.Bund portal, the solution would be a purely technical one and thus easier to provide. The information on the granting date of the MA in question is stored and readily available in the AMIS database. When preparing the submission online, the required data can be accessed directly and the procedure to be followed can be easily determined. An additional query would be sufficient to steer the submission into the applicable procedure track. In contrast to the submission via hard copy, the additional work would be minimal in this case.

It could be argued that for years national change applications and European variations were handled in parallel by the competent authorities. But in that particular instance the

distinguishing lines separating the two groups of MAs were clear-cut and easy to follow. This would no longer be the case if separate provisions were implemented for "old" human medicinal products. With such a measure the current harmonised handling of change applications for veterinary and human medicinal products would be effectively abolished.

But this is not the only disparity to be considered. As soon as the scope of the Variation Regulation is extended to cover national MAs, this special subset of MAs would need to follow different sets of procedures depending on the application. For as soon as a worksharing procedure involving MAs in different MSs is intended, a variation in line with the Variation Regulation is obligatory. At other times, the national provisions would apply. It stands to reason that additional administrative burden would be the consequence.

Even if this would be an acceptable approach for all stakeholders, another issue presents itself. In case the current provisions for change applications were kept for those "old" national MAs, it is to be speculated that the national procedure might be preferred by the applicant´s side. Rather than making use of the newly created worksharing for this subset of "old" national MAs, these procedures might be avoided if suits the applicant. The incentive for the applicant to perform e.g. a worksharing procedure as opposed to a national change application might be reduced. The applicant would have to weigh the respective advantages. The worksharing procedure guarantees a harmonised outcome and a defined approval date for all MAs involved[47]. A national change application has its strength with predominantly shorter time lines until implementation, lower administrative hurdles and for many MAs a favourable fee structure.

Aside from these speculations, it was reported that the BfArM was not inclined to keep a separate procedure for national MAs granted before January 1st, 1998[48]. And this appraisal was confirmed. On December 2nd, 2011 the first draft of the long-awaited amendment to the AMG was published by the Federal Ministry of Health[49]. Among others, the publication included a proposal for the revision of Section 29 relating to the application of changes to MAs.

Surprisingly, the proposed revision was not very far-reaching with respect to content. Apart from of a formal update to Section 29(4), alterations concern sub-sections 2a and 3 as well as the newly introduced sub-section 29(2b). And also, no deviating provisions for MAs granted before January 1st, 1998 are included.

For the category of changes requiring prior approval, revisions were proposed for Section 29(2a) numbers 4 and 6. For the former, the wording of Annex II, number 2(d) of Regulation 1234/2008/EC was transposed in the first half sentence. Interestingly, the term "formulation" was interpreted as "pharmaceutical form". These two terms are not completely interchangeable leading to a shift in meaning. The intention in altering the wording is not quite clear since the change into a comparable pharmaceutical form remains unchanged in number 3 of the section. For the second half sentence of Section 29(2a) number 4 only formal updates were made. In Section 29(2a) number 6 was reduced to the reduction of the waiting period and with this brought in line with Annex II, number 2(k).

Also, for those changes as listed in number 4 of the section, an explicit approval within 90 days by the competent authority was proposed. As explained in the draft, this measure

serves as an approximation to the Type II variation procedure[xxix]. Hence, an exception was made for those changes. The implicit approval following 3 months is upheld for the other changes requiring prior approval as listed in Section 29(2a).

In number 6 of the same sub-section the wording was brought in line with that of Annex II, number 2(k) pertaining to the withdrawal period for veterinary medicinal products.

In the newly created Section 29(2b), the concept of the annual report is introduced. As expected, the included changes eligible for delayed submission are in majority those listed in Annex II, number 1 of the Variation Regulation.

There are minor differences, though. Number 1(a) of Annex II concerning changes of the identity and contact details of MAH or manufacturers was omitted in Section 29(2b). Conversely, when including number 1(b) of Annex II, no exception was made for the tightening of specifications for medicinal products subject to Official Batch Release e.g. for medicinal products derived from human blood or plasma. This change is classifed as a Type IA_{IN} variation in accordance with the Classification Guideline. At the same time, the deletion of a manufacturing site for an intermediate or a site where batch release takes place were not considered to be eligible for an annual report for national MAs.

Apart from these deviations from Annex II, number 1, no additional changes exclusive to national MAs were introduced as being eligible for an annual report.

Section 29	Transposition of	Deviation from wording
2a(4)	Annex II, number 2(d)	"Formulation" interpreted as "pharmaceutical form"
2a(6)	Annex II, number 2(k)	-
2b	Annex II, number 1	number 1(a) not considered number 1(b): manufacuring site of an intermediate and where batch control takes place not considered

Table 8: List of the proposed changes to Section 29 concerning change applications and alignment with the content of Annex II of the Regulation 1234/2008/EC

As given in Table 5, the majority of changes contained in Section 29(2a) are classified as Type II variations on the European level in accordance with the Classification Guideline. At the same time, some Type II variations as listed in Annex II of the Variation Regulation are currently not considered in the AMG. Therefore, the complete list of changes included in Annex II, number 2 of Regulation 1234/2008/EC was not mirrored in this first draft.

The only change proposed for Section 29(3) is the deletion of number 5 concerning the shortening of the withdrawal period. This change is not listed in Annex I of the Variation Regulation as requiring an extension application. Rather, it is classified as a Type II variation in accordance with the Classification Guideline. With the deletion, the classification of the change would be comparable on the national and the European level.

[xxix] Zweites Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften, Referentenentwurf, p.88

Apart from this adjustment, further revisions are not made to sub-section 3. Yet, additional revisions would be required to align this section of the AMG with Annex I of the Variation Regulation.

In the explanatory part of the draft, the Variation Regulation is cited as being the source of the proposed changes[xxix]. Yet this statement does not suffice to clarify the reasons for chosing these particular changes for transposition over others.

The changes in Section 29 also impact changes performed to homeopathic and traditional herbal medicinal products in accordance with Sections 39(2b) and 39d(7) AMG. These medicinal products will continue to lie outside of the scope of the Variation Regulation. With the proposal of the amendment of the AMG these medicinal products would then also benefit from the annual report. This would be offset by the increased number of changes requiring prior approval.

In total, it does not appear to be the intention to implement the provisions of the Variation Regulation for national MAs in Germany at this time. As such, another revision of Section 29 AMG should be required once the scope of Regulation 1234/2008/EC is extended to include the proper reference to the legislation. Yet, the publication of the first draft only signifies the start of the legislative process. Hence it is quite likely that minor or major revisions of the current proposal might become available prior to adoption.

5 DISCUSSION

The current system concerning change applications to purely national MAs granted in Germany is in place for more than two decades now. With the entering into force of the 2nd amendment to the AMG on February 1st, 1987, its basic features were established. Since then, extensive experience was gained. The "Änderungsanzeigen" have proven themselves as lean and efficient in the majority of instances.

There are three basic types of procedures to be followed:

- changes requring no prior approval pursuant Section 29(1),
- changes requiring prior approval pursuant Section 29(2a),
- changes requiring the submission of a MAA pursuant Section 29(3).

For the latter two categories, defined changes are listed in the respective sections. In case a change item is not part thereof, it is to be dealt with in a "tell and do" manner. Since the lists included in Sections 29(2a) and (3) are short, the vast majority of changes do not require prior approval by default. The implementation follows directly after physical receipt of the originally signed submission by the competent authority. This is the most prominent and defining feature of the national system.

In comparison, the variation system for European procedures was introduced with the coming into force of Regulations 541/95/EC and 542/95/EC on March 14th, 1995. This was almost a decade after the national system was established in its current form. As summarised in Figure **1**, there were major updates over time resulting in the doubling of the variation sub-categories from two to four[xxx]. With Regulation 1234/2008/EC, the latest revision entered into force on January 1st, 2010.

The explicit goal of this update to the provisions concerning variations was *to make the regulatory framework covering changes to medicinal products (the 'Variations Regulations') simpler, clearer and more flexible*[50]. As a matter of fact, the Variation Regulation marked a major shift from the former "Type II by default" to a "Type IB by default". This was accompanied by the drafting of relevant guidance documentation to which the classifications of the changes were moved from the regulation. Together with the new procedure pursuant to Article 5 of the Variation Regulation which serves to clarify classifications of unforeseen changes, these measures led to an increase in flexibility of the somewhat rigid variation system.

Alongside these changes, the new concept of implementation prior to submission for minor variations of Type IA and Type IA_{IN} was introduced. The change applications belonging to the former category may even be collected and submitted within one year of their implementation as a so-called annual report.

National change procedures and the European variations existed in parallel for a rather long period of time. But the existence of separate national systems to conducting change procedures was viewed as inacceptable with regards to the otherwise harmonised rules to

[xxx] From Type I and Type II to Type IA, Type IA_{IN}, Type IB and Type II, not counting extension applications

granting MAs[16]. Consequently, appropriate legislation was drafted and implemented with Directive 2009/53/EC to achieve the harmonisation of the way to conducting change applications for all MAs granted in the EEC. A two step process was initiated with this measure. The Member States were to align their national legislation to the provisions as included in Regulation 1234/2008/EC and the EC was to extend the scope of said regulation to MAs granted through national procedures also. In the future, the European variation system is to apply for all MAs regardless of their initial authorisation procedure.

For national MAs in Germany this leads to a dilemma. Even with the improvements of the latest revision, the variation system is still regarded as less efficient and less nimble than its national counterpart in Germany. The main *point de resistance* to the variation system lies in the categorisation of the changes and their application. To match or to improve upon the concept of implementation following submission for the majority of applications as currently in place in Germany is deemed next to impossible.

As had been the case for variation procedures, any change not listed had to be classified in the highest category of the Type II variation. With the ever changing regulatory environment and requirements to the documentation included in the dossier the probability of such an event is high. As an example, a change to the DDPS may be mentioned. This situation was somewhat remedied by setting the default variation category to Type IB when the current Variation Regulation entered into force.

But this is still a far cry from the national system where the reverse reasoning is applied. Only in case a change is identified as significant and requiring prior approval, it is included in either Section 29(2a) or (3). This feature of the national law is quite clever in the respect that it renders the AMG mostly "future-proof" by minimising the number of required amendments.

The European legislation has not reached this state yet. Following its establishment, the legislative basis of the variation system underwent two major revisions (cf. Figure 1). In each instance, the driving force behind the revision was to improve on efficiency and to free up much needed resources. With the legislation currently in place it was again realised that the latter was not fully achieved[xxxi]. As such, it appears that the best possible and most efficient way to introduce changes to MAs by way of variation remains elusive. The optimisation process is ongoing.

As mentioned, the default classification is Type IB for variation procedures. With that, the majority of variations require prior approval albeit an implicit one. This is in contrast to the national system to performing changes in Germany where the majority of changes does not require prior approval. Due to this difference in the general classification, there are also differences in the classification of particular changes.

[xxxi] European Commission, Public Consultation Paper[31], p. 6: *The number of variation procedures for 2011 is expected to double* [for Commission services] *in comparison with 2010. The proliferation of variation procedures is partly explained because marketing authorisation holders are not making use of the possibility to consolidate minor variations in a single annual submission that was foreseen in the Regulation in order to reduce the number of variation procedures.*

As an example, the lack of harmonisation for changes requiring prior approval pursuant Section 29(2a) and changes leading to the submission of a new MAA pursuant Section 29(3) with their counterparts in Annex II number 2 and Annex I in the Variation Regulation is illustrated. 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 Variation Regulation.

This disparity is an effect of the parallel evolution of the national and European legislation with regards to implementing changes. In the AMG the reference to the applicable legislation on the European level was included in Sections 29(4) and (5) for MRP/ DCP and CP, respectively. Yet, their contents appear to have had only minor influence on the sections concerning national MAs thus leading to the present deviant classifications.

All these differences make certain that the extension of the scope of Regulation 1234/2008/EC to national MAs will lead to a significant restructuring in the way national change applications are executed. This need not necessarily viewed as a bad thing, but also grasped as an opportunity.

In addition from the examples given already, there is the concept of the extension of a MA to be considered which is not established on the national level yet. Currently, there is no possibility to add another pharmaceutical form for instance. More importantly, such extensions are automatically incorporated into the global MA pursuant to Article 6 of Directive 2001/83/EC. This should have the consequence that the current national interpretation should also have to be reconsidered in favour of an automatic inclusion into a global MA.

Another counterexample concerns newer developments such as the implementation of the outcome of a PSUR Worksharing Procedure. The result is the harmonisation of the safety relevant sections of the SmPC. Currently, there is no single change item under which the changes may collectively be submitted nationally as is the case for European procedures. Consequently, the update is handled more efficiently on the European level.

The crux of the matter is that the updates often concern sections of the SmPC that automatically lead to a categorisation of the change as requiring prior approval pursuant to Section 29(2a) number 1. In this case the literal interpretation of the AMG is obstructive. Implementing the agreed CSP without changes should be allowed to be submitted as a change application pursuant to Section 29(1) under a single, defined change item. There is no safety risk when adopting a harmonised CSP without changes.

Apart from these considerations, it would be desirable not to completely abandon the national "Änderungsanzeige" but try and preserve a number of its features.

With the publication of the first draft of the revised Section 29 as published on December 2nd, 2011 the willingness to do so was on display. This is due to the fact that the draft refrains from implementing the provisions of the Variation Regulation outright.

For one, the division of changes into those requiring prior approval and those that may be implemented directly following submission is maintained. Consequently, the variation types,

procedures and time lines as established for European procedures would not be introduced into national drug law. The adoption of the proposal in its current form would therefore preserve the separate system to introducing changes for national MAs at least for the time being.

The reasoning behind this minimal transposition can be speculated about. As such it may be the intention to delay any further adoption of the variation system for as long as possible. As soon as national MAs are covered by the scope of the Variation Regulation, variation procedures would need to be submitted obligatorily. But until then, the undisputed advantages of the current legislation can be benefited from.

Already, the starting signal for the legislative process leading up to the revision of the Variation Regulation was given with the publication of a Consultation Paper on September 21st, 2011[31]. If the time between the publication of the first consultation paper[50] and that of Regulation 1234/2008/EC serves as an indication, this process might take more than a year.

For now, only bits and pieces of the content of the Variation Regulation are on display in the first draft. A case in point is the revision proposal for Section 29(2a) number 4. As given before, the different changes as given in Annex II, number 2(d) of the Variation Regulation were included except for the change in formulation. This was exchanged to read pharmaceutical form.

Also, an explicit approval would be introduced for Section 29(2a) number 4 alone if the draft were to enter into force without further revision. For all other changes in this section the implicit approval would be retained.

The introduction of exceptions such as the explicit approval in this instance is usually problematic. Since they tend to increase the administrative burden. In this case, a period of 90 days is slightly different from 3 months[xxxii]. Also, if an explicit approval needs to be issued, the tracking of the procedure would presumably be different than for its implicit counterpart. In case the competent authorities were to decide for reasons of simplification to handle all procedures identically, the purpose of the distinction would be clearly defeated.

The solution could be the generalisation of the explicit approval to cover all changes in Section 29(2a). The advantage of an explicit approval is the higher legal certainty. But in practice, the disadvantage of the delays as observed for variation procedures on the European level may be of importance. In this respect, it is imperative that the current high reliability of the national change procedures be maintained by strictly adhering to the time limit of 90 days. This aspect is paramount to allow for reliable planning on the applicant´s side.

Being able to guarantee reliable time lines is not solely decided on the level of the AMG, though. Rather, a continued effort to increase efficiency has to be embedded in the administrative practice of the involved competent authorities.

In this respect, another national characteristic to be mentioned is the initiation of a change procedure without a validation phase. For national change applications the clock is started as soon as the submission is physically received by the authority. Yet for European variation

[xxxii] equalling 90 to 92 days

procedures, the delay of the start of a variation procedure without cause is seen as a common source of delays. Consequently, this is a feature to be maintained by the German authorities for national applications.

Another aspect to be taken into consideration is the rejection of variations. As soon as the European variation system is established, a shift in the administrative practice that may be overlooked by a superficial glance will take place. As is currently the case, change applications in the lowest change category can not be rejected for national procedures.

This is in contrast to all types of variation procedures. Even for the Type IA variations, there looms the threat of a rejection. If refused, the change should cease to be applied. Of course, this may have far-reaching consequences e.g. in case of a rejection of an increase in batch size submitted in an annual report. Information published by the MHRA states that *a significant number of Type IA notifications have been refused during this period*[xxxiii] *(on average approximately 30%)* [51]. The result of such an approach is some degree of uncertainty on the part of the applicant. Hence, measures should be taken to avoid rejections of these minor variations e.g. by unbureaucratically getting into contact with the applicant for clarification purposes. In the author´s experience this is practised by the BfArM already.

Another example of a pragmatic solution on the national level is the grouping of variations. This concept is not mentioned in the AMG. Nevertheless, grouping of variations is already common practice for national MAs. In particular, there are no restrictions to which changes may be grouped as is the case for European procedures. For such MAs only those changes as listed in Annex III may be grouped according to Article 7 of the Variation Regulation.

For the European variation system it was only introduced with the entering into force of the Variation Regulation on January 1st, 2010. On the European level, grouping was trimmed to allow only the combination of consequential changes. It might have to do with the organisation of the different competent authorities in Europe that unlimited grouping was not introduced. Consequently, more time and effort goes into the preparation of a grouped variation for a European procedure. The reasons are the scrutinisation of the relevant guidance or Questions & Answers documents on authorities´ homepages and liaison with authorities to assure the acceptability of the submission.

Even with the restrictions applying for procedures involving more authorities, the current administrative practice in Germany can be upheld for purely national procedures.
In Article 7(2)(b) of the Variation Regulation there is a loop hole included that may be exploited to circumvent this requirement. It is stated that the grouping of variations may be acceptable *provided that the competent authority of the reference Member State in consultation with the other Member States concerned* [...] *agrees to subject those variations to the same procedure.* For procedures involving national MAs exclusively, only the competent authorities in Germany would need to accept a particular grouping.

Provided the authorities´ continued acceptance of grouping without restrictions, there would be no requirement to change this administrative practice. For this, a renewed commitment from the side of the national authorities is required to continue to accept any groupings.

[xxxiii] 1.1.2010 (coming into force) – 15.11.2010 (date of last modification of the page)

This consent could be communicated by way of an Announcement for instance. Through such a pragmatic approach, the status quo of unrestricted grouping would be maintained.

The capacity of the national competent authorities for creative and pragmatic approaches was also on display with the introduction of worksharing for national MAs via the PharmNet.Bund portal. The second expansion stage of the portal already allows the submission of identical changes for one or more national MAs. At least for the applicant if not for the authorities also, the submission of the identical documentation for different national MAs was greatly facilitated through this measure.

These mentioned simplifications are all not included in the AMG. It stands to hope that even when the provisions of the Variation Regulation have to be followed such pragmatic measures would be kept and possibly extended. In sum they significantly influence the throughput and speed of the procedures. Through this, parts of the identified disadvantages of the European variation system may be offset.

With the acceptance that harmonising the procedures to conducting change procedures is inadvertible and only a question of time, another perspective presents itself. The initiated review of the Variation Regulation may be used to try and change the way to conducting variations. With the grouping for instance, a national feature was already established on the European level.

The possibility to refine the variation system might be accomplished with the scheduled review. This is actually a built-in feature of the Variation Regulation. In Article 26 it is explicitly demanded that in the year 2012 *the Commission services shall assess the application of this Regulation as regards the classification of variations, with a view to proposing any necessary amendments to adapt Annexes I, II and V to take account of scientific and technical progress.*

This initiative may also play a part in the procedure to extend the scope of Regulation 1234/2008/EC to include national MAs. As given in the recently published Consultation Paper, it is the intention to adjust *some of the procedures with a view to focus resources of the authorities on variations with the most impact on public health* [31] among other work assignments.

This could include the establishment of the concept of the comparable pharmaceutical form on the European level. The conversion into a comparable pharmaceutical form should be handled within the scope of a variation application. Arguments that the documentation to be reviewed as being too extensive are short-sighted. There are other changes classified as variations that also require the assessment of copious amounts of documentation, such as the application for a new indication.

Also, the current national practice of adding information to the safety-relevant sections of the SmPC[xxxiv] based on pharmacovigilance findings in a “tell and do” procedure would be a candidate. Additions of safety-relevant information may be exempt from the requirement of conducting a Type II variation. Not every change in the pharmacovigilance profile of a medicinal product is drastic and sudden thus warranting a USR. With an appropriate update in

[xxxiv] Sections 4.3 to 4.9

the Classification Guideline, swift distribution of the upated product information would be ensured. When initially drafting the Regulation 1234/2008/EC there had been a similar proposal from the side of industry associations that was not considered at that time[47].

In total, the classifications for the single changes included in the Classification Guideline should be re-evaluated. For this task, the experience gained with the current provisions as laid down in the Variation Regulation should be used. Over a period of almost two years now, insights were gained and an understanding formed which of the classifications for variations might be down-graded. In light of the long experience with the national system to handling change applications in Germany the effort should be renewed to further liberalise the classifications.

6 CONCLUSION AND OUTLOOK

The path ahead is clear. It leads to the intended European harmonisation of the procedures to applying for and handling of changes to existing MAs. The process of attaining that goal is steered by the appropriate legislation already in place.

Once the scope of the Variation Regulation is extended to national MAs there will no longer be no room for separate provisions in national drug law.Cherished national provisions may only be preserved unless they are in line with the law or not covered by it at all. This includes unlimited grouping or the lack of a validation phase, respectively.

Hence, the effort should be shifted towards remodelling the European system. For the year 2012 a review of the Variation Regulation is scheduled. The main focus should be placed on a re-evaluation of the suitability of the classifications in the accompanying guidance. In a number of cases, changes might be re-classified as belonging to a lower variation category.

On this occasion the advantages of the national system currently in place in Germany should be communicate again. The merits may be identified more readily now following 2 years of operating experience with the revised variation system.

Still, it is expected to be a long and rocky road requiring persistency and persuasive power from the side of the involved parties.

7 SUMMARY

Change applications for marketing authorisations (MAs) granted solely in Germany follow separate procedures as do variations in European procedures such as MRP, DCP or CP. The national and European systems to applying for and implementation of changes to existing MAs evolved in parallel and rather independently for a long period of time. The legal basis is Section 29 of the Medicinal Products Act ("Arzneimittelgesetz", AMG) for national MAs and Regulation 1234/2008/EC (Variation Regulation) for MAs granted in European procedures, respectively.

Yet, the continued existence of separate provisions to conducting change procedures was regarded to be in blatant contrast to the harmonised rules to applying for an initial application for MA. With Directive 2009/53/EC amending Directives 2001/82/EC and 2001/83/EC relating to veterinary and human medicinal products, this deficit was addressed. Through said Directive, the European Commission was empowered to take appropriate measures to extend the scope of the Variation Regulation to purely national MAs also. In consequence, the national legislation as currently in place in Germany is to be substituted by the provisions pertaining to the conduct of variation procedures in the near future.

This represents a major shift in the practice of introducing changes to national MAs in Germany. A detailed comparison of the procedure types reveals similarities as well as subtle though decisive differences in the procedures. For instance, the procedure type to be followed by default can be approximated as Type IA_{IN} nationally as opposed to Type IB for MAs falling under the scope of the Variation Regulation. This has far-reaching consequences since an approval prior to implementation of the change is not required for the majority of national changes in contrast to variation procedures. As a result, the time until implementation of the change is on average significantly longer for a variation.

This is intensified by the large number of changes listed in the *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* (Classification Guideline) that are classified as Type IB and Type II variations. In these variation categories, an implicit or explicit approval is required, respectively. In contrast, only for a select and small number of changes listed in Sections 29(2a) AMG, an application requiring prior implicit approval has to be submitted.

In practice, delays at different stages of the variation procedures, such as during validation or clock-stops are observed for variations thereby leading to unreliable time lines for the applicant. Currently, only an implicit approval and no clock-stop are foreseen for national change applications pursuant to Article 29(2a). This requires the national competent authorities to strictly adhere to the time line of 3 months.

Another distinctive feature of the national procedures is the absence of the possibility of its rejection for change applications requiring no prior approval. The opposite is the case for variations. For all the variation types there is the possibility of a rejection of the application. As a result of all the differences, current national procedures for applying for changes allow

for higher reliability and predictability of the time lines as their counterparts on the European level.

Apart from the differences in the procedures *per se*, there are also quite significant deviations with respect to the classification of certain changes. As such, changes requiring the submission of anew MA application nationally may be treated within the scope of a Type II variation on the European level and vice versa. Cases in point are the addition of an indication outside the approved area of therapy and the conversion into a comparable pharmaceutical form. In this respect, harmonisation truly is to be welcomed.

As becomes clear from these examples, the expansion of the scope of the Variation Regulation as triggered by the provisions included in Directive 2009/53/EC will have far-reaching consequences for the conduct of change applications for purely national MAs in Germany. Yet, this may also be greeted as an opportunity in some instances. In particular, this concerns the facilitated application of indications outside the approved area of therapy and the introduction of the concept of the extension application. The latter is linked to a possible review of the restrictive national interpretation of the global MA. Furthermore, a procedural simplification and reduced fees are expected of an update of the safety-relevant sections of the SmPC and PIL following a PSUR Worksharing Procedure.

At the same time, the conversion into a comparable pharmaceutical form within the scope of an application requiring prior approval will no longer be possible if not included in the legislation at a later stage. Also, for the addition of safety-relevant information to the SmPC and PIL an approval will then have to be awaited instead of the current “tell and do” approach for national MAs.

On December 2nd, 2011 the first draft of the revision of Section 29 was published. In the scope of the proposal, the adoption of the variation system as laid down in the Variation Regulation was not included. Only certain aspects such as the annual report for a number of defined changes as well as extended requirements for the submission of changes in accordance with Section 29(2a) are included. It appears to be the intention to postpone the adoption of the variation procedures until the scope of the Variation Regulation is extended appropriately. Also, there is no implementation of deviating provisions for MAs for human medicinal products authorised before January 1st, 1998 as given in Directive 2009/53/EC forseen. Full harmonisation with the European variation system is aimed for.

Apart from these considerations, it is desirable not to fully abandon the benefits of the national “Änderungsanzeigen”. This involves maintaining current administrative practices of the national competent authorities. Since they are not necessarily anchored in the AMG, they are not required to be changed with the legislative revision. This would include forgoing a formal validation phase and continuing to start the procedure directly following receipt of the application. Also, there is the possibility to preserve unlimited grouping as currently practiced. Such an approach would not contradict the provisions given in the Variation Regulation provided it is limited to national German MAs. Only the willingness to do so would need to be communicated. These two measures alone are predicted to shorten the processing time of applications involving national German MAs in relation to variation procedures as practised currently on the European level.

Aside from retaining such pragmatic administrative practices, the opportunity should be seized to refine the variation system by re-evaluating the appropriateness of variation classifications as listed in the relevant guidance. In the two years of experience with the provisions of the Variation Regulation, sufficient insights should have been gained as to which changes may be eligible to be downgraded. As an opportune time to do so the upcoming revision of the Variation Regulation slated for 2012 presents itself. At that time it should also be strived to establish certain concepts such as the comparable pharmaceutical form on the European level.

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

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