A critical review of the current marketing authorisation transfer procedure in Europe

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Gilda Gordon
aus Buenos Aires

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Betreuer und 1. Referent: Dr. Petra Bettauer

Zweiter Referent: Dr. Rose Schraitle

A mis hijitos queridos, Tobias y Tanja

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List of Abbreviations

CA	Competent authority
CAP	Centrally authorised product
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human
CP	Centralised procedure
DCP	Decentralised procedure
DDPS	Detailed description of the pharmacovigilance system
eCTD	electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
INN	International Non-proprietary Name
MAH	Marketing authorisation holder
MRP	Mutual recognition procedure
NCA	National competent authority
QPPV	Qualified person for pharmacovigilance
RMP	Risk Management Plan
RMS	Reference member state
SmPC	Summary of product characteristics
XEVMPD	Extended EudraVigilance Medicinal Product Dictionary

1 Introduction

In order to market a medicinal product in the European Economic Area (EEA), a product must have a marketing authorisation issued by one of the EEA competent authorities (Article 6 Directive 2001/83/EC [1]).

A competent authority issues a marketing authorisation after evaluation of a submitted dossier, taking into account the Quality, Safety and Efficacy of the medicinal product. If the benefits outweigh the risks, the marketing authorisation is granted.

This marketing authorisation is issued to a natural or legal entity (company) called the "marketing authorisation holder" (see section 1.2).

After authorisation, any changes made to the approved dossier, including the approved Product Information (Summary of Product Characterisitics (SmPC), Package Information leaflet and Labelling), must be notified to the competent authorities of the member states where the medicinal product is authorised.

These changes are defined as "variations" and are regulated in the Commission Regulation (EU) No. 1234/2008 [2], amended by Commission Regulation (EU) No. 712/2012 [3].

However, not all possible changes are within the scope of the Variation Regulation. One such change is this thesis' topic: the marketing authorisation transfer.

This thesis will describe what a marketing authorisation transfer is and why it is not included in the Variation Regulation and will review the current procedures for marketing authorisation transfer of human medicinal products in the 30 EEA member countries (the 27 European Union member states (correct to June 2013) plus Liechtenstein, Iceland and Norway) by comparing the main significant aspects of the procedure from the applicant's perspective, such as required documentation and timelines. The results are generally tabulated for easier comparison.

The implications for the applicant of the current situation will be discussed, taking into consideration various changes which are often consequent from a marketing authorisation transfer, followed by possible proposals for change.

The transfer of orphan designation associated with the marketing authorisation transfer for orphan medicinal products will not be discussed (Q. 15.10 of EMA's "Post-authorisation procedural advice for users of the centralised procedure" [4]).

Croatia, which joined the European Union on 1 July 2013, has not been included in the list of EEA countries compared.

1.1 Variations and other changes

As seen before, any changes made to a medicinal product after authorisation must be notified to the authorities.

Most changes (variations) are regulated in the amended Commission Regulation (EU) No. 1234/2008 [5] (the "Variation Regulation") which from 4 August 2013 will apply to all medicinal products, regardless of the procedure by which they were authorised: purely national, mutual recognition, decentralised or centralised procedure.

The variations are classified in the "Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products …" [6] (the "Classification Guideline"). Variations are classified into 3 main types: type IA, type IB and type II. In addition, specific changes defined in Annex I of the Variations Regulation are considered "extensions" (such as change to the strength or pharmaceutical form of a medicinal product).

This classification is important as it determines whether a variation requires approval in order to be implemented. The Classification Guideline lists variations which have been categorised and details the conditions to be met for type IA and the documentation to be submitted for type IA and type IB variations.

Further guidance for purely national, mutual recognition and decentralised authorised products is provided by the CMDh's "Best Practice Guides for the submission and processing of Variations in the Mutual Recognition Procedure" [7] and in the CMDh's Questions & Answers on Variations [8].

For centrally-authorised products guidance is found in EMA's "Post-authorisation procedural advice for users of the centralised procedure" [4], where further information is provided on how a variation has to be submitted and how it is processed.

Not all possible changes, however, are within the scope of the Variation Regulation or included in the Classification Guideline.

Article 61(3) (of Directive 2001/83/EC [1]) may be applied for changes to the package leaflet and/or labelling which do not affect the Summary of Product Characteristics.

The transfer of a marketing authorisation (this thesis' topic) is not included in the Variation Regulation [5], as stated in Article 1(2): "This Regulation shall not apply to transfers of a

marketing authorisation from one marketing authorisation holder (hereinafter holder) to another".

Changes in the local representative and change in the legal status of a medicinal product are other changes which are not included in the Variation Regulation and are nationally handled.

For other changes not detailed in the Guideline nor dealt with nationally or via the Article 61(3) procedure, the marketing authorisation holder may submit these changes as a Type IB variation ("type IB unforeseen variation") or request a recommendation on classification via the Article 5 (of the Variation Regulation [5]) procedure from the relevant national competent authority for a purely national marketing authorisation, the reference member state for MRP/DCP products or, for centrally-authorised products, from the European Medicines Agency.

1.2 Marketing authorisation transfer

1.2.1 Introduction

A transfer of a marketing authorisation is "the procedure by which the marketing authorisation is transferred from the currently approved Marketing Authorisation Holder to a new Marketing Authorisation Holder which is a different person/legal entity**"** (Q. 15.1 EMA's "Post-authorisation procedural advice for users of the centralised procedure" [4]).

The marketing authorisation holder, who must be "established in the Community", is "responsible for marketing the medicinal product" and has the "civil and criminal liability as provided for by the law of the member states" for the medicinal product (Articles 8, 6 (1a) and 25 of Directive 2001/83/EC [1])

The marketing authorisation holder is responsible throughout the life of the medicinal product concerned, which includes taking into account any technical and scientific progress and making amendments as necessary. Amongst the most important tasks are those concerning the pharmacovigilance of the medicinal products they place on the market. There may also be post-authorisation commitments that have to be fulfilled, such as post-authorisation safety studies, follow-up measures or specific obligations.

The responsibilities of a marketing authorisation holder are detailed in Articles 23, 23a and 24 of Directive 2001/83/EC [1].

In the marketing authorisation transfer procedure the marketing authorisation is transferred to a different person/legal entity, while a change (in the name and/or address) of the marketing authorisation holder when the legal entity remains the same is included in the Variation

Regulation (defined as an administrative type IAIN no. A.1 variation in the Classification Guideline [6]).

The marketing authorisation transfer procedure results in the original marketing authorisation holder's rights and responsibilities concerning the specific medicinal product to be transferred to the new marketing authorisation holder on a specific date on which the transfer is effected.

This means that the medicinal product authorised to the new marketing authorisation holder is authorised under exactly the same conditions as previously:

- it must be manufactured and controlled according to the authorised dossier
- the product must be placed on the market within 3 years of the original authorisation date in the member state where it is authorised ("Sunset Clause") to avoid cessation of the marketing authorisation [9]
- its expiry date is the same and therefore, if applicable, the date by which it has to be renewed in order to remain valid
- any post-authorisation obligations must be fulfilled as before, as applicable: Periodic Safety Update Report data lock points, follow-up measures and special obligations.

A marketing authorisation transfer may be necessary as a result of a company (the current marketing authorisation holder) selling its product to another company (another legal entity) or as a result of a merger or acquisition, when one marketing authorisation holder is taken over by another company, such that the original company ceases to exist as a separate legal entity.

This change is relatively common: in the 10 year period from 2000 to 2010 the number of announced mergers and acquisitions worldwide in the biotechnology and pharmaceutical sector per annum rose from around 600 in the year 2000 to around 1000 throughout the period 2005-2010 [10].

By definition, only the change of marketing authorisation holder as a legal entity (the marketing authorisation holder's name and contact details) is submitted in the marketing authorisation transfer procedure. Any other changes which may have to be made as a consequence of the marketing authorisation transfer, such as a change in the name of the medicinal product, the introduction of a new Pharmacovigilance System and Qualified Person for Pharmacovigilance, a change in the local representative or a change in manufacturer(s), must usually be submitted separately – more details are given in section 3.

1.2.2 Legal basis of the marketing authorisation transfer

As seen in section 1.1, the marketing authorisation transfer change is outside the scope of the Variation Regulation [5] and is therefore processed individually by the competent authority which granted the marketing authorisation, regardless of the procedure by which the product was authorised (purely national, mutual recognition, decentralised or centralised).

A summary table of the legal basis of the marketing authorisation transfer for the EEA member states is found in Appendix 2.

Some guidance concerning marketing authorisation transfers is found in Questions 2.8 and 3.12 of CMDh's Questions & Answers on Variations [8].

For centrally-authorised products, the marketing authorisation transfer must comply with Commission Regulation (EC) No 2141/96 [11]. Further guidance is found in section 15. of EMA's "Post-authorisation procedural advice for users of the centralised procedure" [4].

1.2.3 Reasons for the marketing authorisation transfer not being included in the Variation Regulation

The amended Variation Regulation [5] is the result of efforts to harmonise procedures in Europe which started before 1995. This was preceded by many discussions between the stakeholders (European Union (EU) member states' competent authorities and industry).

Unfortunately, on the topic of the marketing authorisation transfer, harmonisation could not be reached.

A marketing authorisation is required to market a medicine in one, several or all EEA member states.

However, Directive 2001/83/EC [1] and Regulation (EC) No 726/2004 [12] contain no definition of what a "marketing authorisation" is, only the elements to be submitted in order to be issued one by a competent authority.

Consequently, different member states define "marketing authorisation" differently and the issued marketing authorisation number may be issued per individual strength / pharmaceutical form / pack size of a medicinal product, for a combination of these or for all strengths / pharmaceutical forms / pack sizes of a medicinal product. How the marketing authorisation and marketing authorisation number is issued also depends on the marketing authorisation procedure (whether the product is centrally-authorised or nationally authorised) [13].

This means that a marketing authorisation transfer may result in a new marketing authorisation number being issued for the transferred marketing authorisation (such as in

Ireland and the United Kingdom) or not (e.g., Germany), depending on the member state concerned.

How a marketing authorisation transfer is processed also differs greatly from one member state to another (see section 2.2) and no agreement could be reached on one harmonised marketing authorisation transfer procedure [14].

2 Comparison of the marketing authorisation transfer procedure in Europe

In this section the most significant elements from the applicant's point-of-view of the marketing authorisation transfer procedure (requirements, evaluation, timeline and implementation) are reviewed, compared and discussed for the 30 European Economic Area (EEA) member states [15] and at the European Medicines Agency (EMA) (for the centralised procedure).

2.1 Methods

2.1.1 Searching competent authorities' websites

In order to obtain information in English about the marketing authorisation transfer procedure, the competent authorities websites in all the EEA member states and the EMA website were searched, mostly using "transfer" as the search term, sometimes supplemented by "marketing authorisation holder" or "variations".

In a couple of websites information was found in the national language once the translated term for "transfer" was used, such as in Austria („*Übertragung*" in German) and Portugal and Spain („*transferencia*"). This information was translated using a free online translator (such as the Google translator tool [16]) in order to have some idea of the national competent authorities' requirements.

In some websites the information was found indirectly, such as in Finland where a link to relevant information was included in an e-mail reply.

2.1.2 Requesting further information

If no or insufficient information was found, an e-mail in English was sent to the national competent authorities requesting it.

As general information was requested and no specific medicinal product was concerned, no direct competent authority contact was available and therefore the e-mail addresses published in the CMDh Contact Points spreadsheet [17] ("Advice on MRP & DCP procedures" version available in March 2013) and from the national competent authorities websites were used.

The information requested in the e-mail sent to the specific national competent authority was based on the information available in English.

Where possible, some results were confirmed by telephone or e-mail with the national competent authorities.

2.1.3 Other

The results obtained were supplemented by IDRAC [18] regulatory summaries (Appendix 5).

2.1.4 Comparison of results obtained for the competent authorities

The results obtained were reviewed for different elements (such as documentation required and timeline) separately and tabulated for easier evaluation of similarities and differences where appropriate.

2.2 Results

The results obtained as detailed in section 2.1 were summarised to review various marketing authorisation transfer elements.

For simplification, the two-letter abbreviation for the Member State (Appendix 1) stands for the national competent authority in the summary tables, except for "EMA" for the European Medicines Agency for centrally authorised products.

In Germany, the two competent authorities for human medicinal products are included: the the Federal Institute for Vaccines and Biomedicines, also known as the Paul Ehrlich Institute (PEI), responsible for particular medicinal products such as allergens, Advanced Therapy Medicinal Products and vaccines [19], and the Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM) [20], for all other medicinal products.

Results for Liechtenstein are not shown, as Liechtenstein accepts marketing authorisations granted by Austria, as long as the applicant had applied for a marketing authorisation for Liechtenstein in the MRP/DCP application [15].

National competent authority website links have been tabulated in Appendix 6.

The results obtained are correct to June 2013. Legislation and competent authority websites are regularly updated and therefore individual items may change. However, as the intention of this review is to compare the procedure within the EEA, this is considered representative of the marketing authorisation transfer as currently encountered by applicants.

2.2.1 Comparison of the marketing authorisation transfer in the EEA

Being a procedure which is nationally handled, it is expected that different aspects will differ between the competent authorities.

Elements which differ are:

- the availability of information in English in the competent authorities' websites
- who should submit the marketing authorisation transfer application (the current or the future marketing authorisation holder)
- the timing of the marketing authorisation transfer submission (whether the transfer application may be submitted before the marketing authorisation has been granted or only after)

- documents required for submission of a marketing authorisation transfer application
- evaluation, timeline and implementation of the marketing authorisation transfer
- possibility of grouping marketing authorisation transfer applications
- clearing of stock from the previous marketing authorisation holder
- submission of additional changes (whether other changes, such as product name change, change in the pharmacovigilance system or change of the local representative, may or must be submitted in parallel to the marketing authorisation transfer application)
- fees to be paid

This thesis will compare the more significant aspects of a marketing authorisation transfer submission in the EEA:

- documents to be submitted
- evaluation, timeline and implementation

2.2.2 Documents required for submission of a marketing authorisation transfer application

The marketing authorisation transfer application is submitted only in the member state concerned as this is a national procedure.

However, for mutual recognition and decentralised procedures, the Reference Member State must be notified of the change (Q. 2.8 CMDh Questions & Answers on Variations [8]).

For products authorised via the centralised procedure, the application is submitted to the European Medicines Agency only.

The documents to be submitted as part of the application are discussed below.

2.2.2.1 Results for marketing authorisation transfer documentation requirements

An overview of the main marketing authorisation transfer submission documents for authorised products has been tabulated in Appendix 3, based on the search done as detailed in section 2.1.

The information and documents requested concern:

- the medicinal product (name, marketing authorisation number, marketing authorisation issue / expiry date)
- the marketing authorisation transfer (current and proposed marketing authorisation holder, effective date) and
- the proposed marketing authorisation holder's ability to take over responsibility for the product (that it has in its possession the up-to-date and complete dossier and information concerning any additional obligations, information on the Pharmacovigilance System and the Qualified Person for Pharmacovigilance (QPPV))

All applications must consist of:

1. a cover letter
2. proof of establishment of the future marketing authorisation holder (as proof that the MAH is established in a EEA member state) (with a few exceptions such as Finland)
3. updated product information (SmPC, package leaflet and labelling) showing the tracked changes of marketing authorisation holder name and address (in some competent authorities accompanied by a declaration that no other changes apart from those concerning the marketing authorisation transfer or submitted together with it (such as change of legal representative) have been made)
4. mock-ups (if applicable)

5. proof of payment – when applicable (when there is a fee that must be paid before submission)
6. power of attorney, if applicable

This review will discuss the main documents to be submitted in the application: the application form and documents demonstrating the proposed marketing authorisation holder's ability to take over responsibility for the product.

2.2.2.1.1 Application form

Whether an application form is used and if so, which, depends on the competent authority. Details are found in Appendix 3.

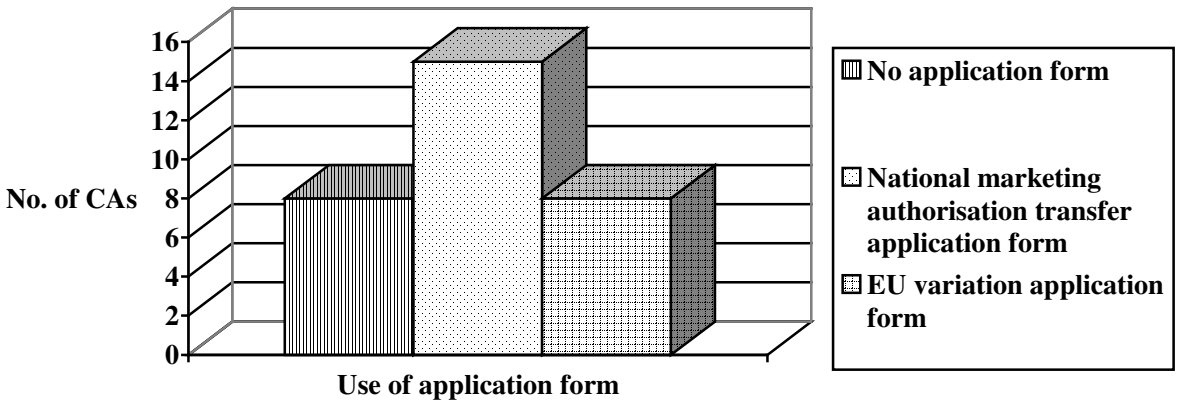
For simplification, a table detailing the use of application forms for the marketing authorisation transfer application in the competent authorities is found below.

Table 1 Use of application form for marketing authorisation transfer applications

Use of application form	Competent authorities (CAs)	No. of CAs
No application form	FI, FR, IT, NL, PL, PT, SI, EMA	8 (26%)
National marketing authorisation transfer application form	AT*, BG, CZ, DE (BfArM, PEI*), EL, HU, IE, LT*, LU*, MT, RO, SE, SK, UK	15 (48%)
EU-Variation application form	BE, CY, DK, EE, ES* (EU-VAF in ES), IS, LV, NO	8 (26%)
	Total	31

* not available in English

Figure 1 Summary of the use of an application form for marketing authorisation transfer applications



From table 1 can be seen that a quarter of the competent authorities do not require the submission of a marketing authorisation transfer application form but that nearly three-quarters of the competent authorities do.
It is interesting to note that a quarter of the competent authorities request the use of the EU Variation Application Form [21] for submission of a (national) marketing authorisation transfer application. However, nearly twice the number of competent authorities use a national marketing authorisation transfer application form rather than the EU variation application form.

Amongst the member states requiring the submission of the EU Variation Application Form, the change is classified differently (see below).

Although in most competent authorities the application forms are available in English, in Austria, Germany (PEI), Lithuania and Spain the forms are available only in the local language.

Use of EU Variation Application Form

The category of change which must be ticked in the EU variation application form for competent authorities which request its use is summarised in table 2 below (from Appendix 3).

Table 2 Categorisation of marketing authorisation transfer change in the EEA member states using the EU-variation application form for submission

Classification of MA transfer change	CAs	No. of CAs
Type IA	BE	1
Type IB	DK, NO	2
Type II	CY, EE, ES, LV	4
Not classified	IS	1
	Total	8

From table 2 it can be seen that the change is categorised differently by these competent authorities: type IA, type IB and type II.

The type of change which is marked in the form, however, is not necessarily an indication of how that competent authority deals with the procedure. For further discussion, see section 2.2.3.3.

2.2.2.1.2 Proposed marketing authorisation holder's ability to take over responsibility for the product

The owner of the marketing authorisation for the specified product is the current marketing authorisation holder (MAH), who can market it but also has responsibilities and obligations. When the marketing authorisation is transferred, both the rights and obligations are transferred to the new MAH. For this reason, some competent authorities require a "waiver declaration" from the current marketing authorisation holder, where the current MAH cedes its rights to the new MAH from a specified date (see 2.2.2.1.4 below).

Sometimes competent authorities require a "transfer declaration" where the proposed MAH declares that it takes upon itself all MAH duties and responsibilities from a specific date and sometimes a "transfer agreement" must be submitted, which includes the waiver declaration of the current MAH and the transfer declaration of the proposed MAH.

In order for the new MAH to be able to fully comply with its obligations, it must have available the complete updated dossier for the product and information regarding supplemental obligations (such as follow-up measures, special obligations, risk minimisation activities, paediatric obligations). A declaration from the current MAH that this has been or will be provided and/or from the proposed MAH that this information has been transferred is often required.

Results for declarations requirements for marketing authorisation transfer applications

From the results in Appendix 3, it can be seen that nearly all the competent authorities require submission of declarations, with the exception of Germany (BfArM and PEI) and Sweden.

A summary of declaration requirements from Appendix 3 is found in table 3 overleaf.

Table 3 Declarations requirements for marketing authorisation transfer applications

Declaration required	Competent authorities (CAs)	No. of CAs
Waiver (from current MAH)	AT, CY, FR, HU, IE*, IS, MT*, NL, PL, SI	11
Declaration that proposed MAH agrees to MA transfer	AT, BG*, CY, CZ*, EL*, FR, HU, IE*, IS, LV, MT*, NL, PL, SK*	13
Transfer of dossier for product concerned will/has been done (from current MAH)	BG*, CY, CZ*, EL*, IE*, LT, MT*, PT, SI, SK*	9
Transfer of dossier for product concerned will/has been done (from proposed MAH)	AT*, BG*, CY, CZ*, EL*, IE*, LV, MT*, PT, RO, SK*, UK, EMA*	12
Transfer agreement between both parties	BE, CY, DK, EE, ES, FI, IT, LU, NO, PL, SK	11

* template available

Some member states require more than one type of declaration (for example, Bulgaria and Ireland) and some competent authorities provide templates for these declarations (8 from the 28 competent authorities which require additional declarations), but most do not.

2.2.2.1.3 Pharmacovigilance System

Amongst the most important responsibilities of a marketing authorisation holder is to "operate a pharmacovigilance system for the fulfilment of his pharmacovigilance tasks" and to "have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance" who is "responsible for the establishment and maintenance of the pharmacovigilance system" (Article 104 of Directive 2001/83/EC [1]). Final responsibility always rests with the marketing authorisation holder.

If the pharmacovigilance system changes with a change of marketing authorisation, this must be submitted as a variation (see section 3). In addition, from the table in Appendix 3, it can be seen that about half of the competent authorities require information about the pharmacovigilance system to be submitted with the marketing authorisation transfer application, especially the QPPV contact details.

2.2.2.1.4 Effective date

It is very important for the date when the new marketing authorisation holder takes over all the responsibilities and obligations for the medicinal product to be clear to all parties: the current and future MAH and the competent authority concerned.

This (implementation) date is sometimes called the “effective date” as it is the date on which the marketing authorisation transfer takes effect.

The effective date is usually taken to be on or after the date when the change is authorised. As the timeline to approval differs from one member state to another (see section 2.2.3.2), this must be taken into account when requesting the effective date.

It is generally possible for the effective date to be determined by agreement between the current and proposed marketing authorisation holders and the competent authority concerned and therefore it is important for it to be clearly stated. Where it should be stated (cover letter, application form, declarations) depends on the competent authority concerned.

2.2.3 Evaluation, timeline and implementation of the marketing authorisation transfer

As the marketing authorisation transfer procedure is a national procedure, different member states may evaluate the application differently. How long this evaluation takes may also vary. This timeline has implications regarding when the change may be implemented.

2.2.3.1 Results for evaluation of the marketing authorisation transfer application

The results for evaluation obtained from the search as detailed in section 2.1 are summarised in table 4 below (sources in Appendix 4).

Table 4 Evaluation of marketing authorisation transfer applications

	Competent authorities (CAs)	No. of CAs
No approval required	AT, DE (BfArM, PEI)	3
Approval required	BE, BG, CY, CZ, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK, EMA	28
	Total	31

From table 4 it can be seen that differences exist in how the marketing authorisation transfer change is evaluated.

In a couple of member states no approval is required (Austria and Germany), but in general approval is required before the change can be implemented (the product sold with the new marketing authorisation holder’s name and address).

2.2.3.2 Results for the marketing authorisation transfer timeline

The timeline refers to how long it takes for a marketing authorisation transfer application to be evaluated and authorised (if applicable) in order for the transfer to be implemented. The results for the timeline are tabulated overleaf.

Table 5 Timeline of the marketing authorisation transfer procedure

	CA	Timeline from receipt of notification	Reference
1	AT	Immediate, unless otherwise requested	[87]
2	BE	30 days	[93]
3	BG	30 days (+ 30 if documentation incomplete)	[95]
4	CY	3 – 6 months	[99]
5	CZ	30 days (+ 30 if documentation incomplete)	[104]
6	DE (BfArM, PEI)	Immediate, unless otherwise requested	[61]
7	DK	30 days	[116]
8	EE	60 days	[63]
9	EL	*Information not available*	-
10	ES	"No fixed deadline but MA transfers usually take a month, following order of reception"	[120]
11	FI	120 days	[125]
12	FR	60 days	[67]
13	HU	30 days	[128]
14	IE	6 weeks	[129]
15	IS	30 days	[136]
16	IT	90 days	[137]
17	LT	30 days (+30 if documentation incomplete)	[73]
18	LU	1 – 2 months	[143]
19	LV	60 days	[144]
20	MT	60 days	[146]
21	NL	60 days	[148]
22	NO	90 days	[151]
23	PL	30 days	[79]
24	PT	60 days	[80]
25	RO	60 days (30 for review after confirmation of payment of fees + 30 to issue decision)	[81]
26	SE	90 days	[156]
27	SI	60 days (30 for review of validity + 30 for approval of MA transfer)	[83]
28	SK	30 days (+30 if documentation incomplete)	[165]
29	UK	6 weeks	[166]
Average		**49 days (7 weeks)** (excluding CY)	
Minimum - maximum		**Immediate with arrival of notification – 6 months**	

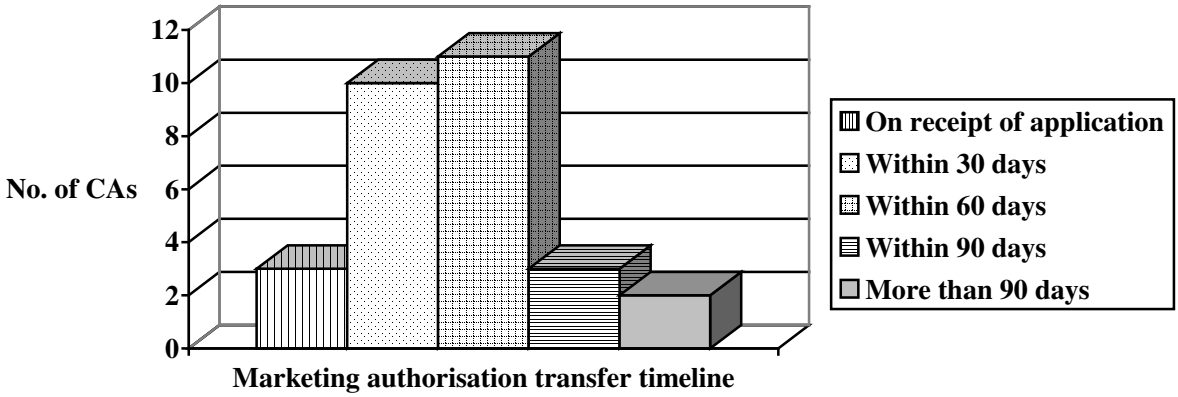
CA	Timeline	Reference
EMA	Authorisation of the transfer is from the date of the notification of the Commission decision (30 days for finalisation of EMA opinion + time until the European Commission decision is issued). If a name change is involved, the name change application should be submitted 4-6 months before the planned marketing authorisation transfer submission date as Name Review Group approval for the proposed name is required.	[4]

For easier comparison, the results are summarised in table 6 overleaf.

Table 6 Summary of the timeline for the marketing authorisation transfer procedure in the EEA member states

Marketing authorisation transfer timeline	Competent authorities (CAs)	No. of CAs
On receipt of application (unless otherwise agreed with NCA)	AT, DE (BfArM, PEI)	3 (10%)
Within 30 days	BE, BG, CZ, DK, ES, HU, IS, LT, PL, SK	10 (34%)
Within 60 days	EE, FR, IE, LU, LV, MT, NL, PT, RO, SI, UK	11 (38%)
Within 90 days	IT, NO, SE	3 (10%)
More than 90 days	FI, CY	2 (7%)
Information not available	EL	1
	Total	29 (excluding EL)

Figure 2 Summary of the timeline for the marketing authorisation transfer procedure in the EEA member states



In the majority of member states the marketing authorisation transfer takes between 1 to 2 months. Only in two member states (Austria and Germany) can the transfer be implemented on receipt of the application, while in 5 member states implementation takes 3 months or more (table 6 above).

2.2.3.3 Implementation of the marketing authorisation transfer change

Implementation of the marketing authorisation transfer, i.e., selling the medicinal product concerned with the name of the new marketing authorisation holder in the product information texts, may generally be done after approval (if required) (section 2.2.3.1) from the effective date (section 2.2.2.1.4) requested in the marketing authorisation transfer application. As seen in the timeline section above (section 2.2.3.2), time to approval varies between member states.

A few member states give a time limit by which the change should be implemented, such as Denmark and Poland (no later than 6 months after authorisation) [114, 79] and France (the marketing authorisation transfer should be implemented as soon as possible) [67].

The difference in timeline for the member states, ranging from immediate with receipt of the application to 6 months, complicates planning the implementation after approval when different member states are involved, such as for a MRP/DCP product. This means that when such a product is transferred in several member states, as the transfer will not be concluded in all member states concerned at the same time, very clear contractual arrangements must be agreed upon between the current and future MAHs, delineating the various responsibilities during the transitional period, such as batch release and submission of regulatory activities, like variations [4].

Care must be taken not to assume a correlation between the extent of documentation required, evaluation and timeline. One could assume that little documentation would indicate a shorter timeline (and vice versa), but examples like that of Finland and Sweden (few documents but 4 and 3 months for approval respectively) and that of Poland and Romania (extensive documentation, one month for approval), show that this is not necessarily the case.

Care must also be taken with how a competent authority categorises the marketing authorisation transfer change where the EU variation application form is used, evaluation and timeline and that for the same category in the "Variation Regulation" [5]. For example, the marketing authorisation transfer in Belgium is categorised as a "type IA" change, but unlike type IA notifications, requires approval before implementation which takes 1 month and in member states where it is categorised as a "type II" change, the timeline ranges from 1 month (Spain) to up to 6 months (Cyprus), whereas standard type II variations take 2 months.

2.2.4 Electronic submission of the documentation

In most member states the submission may be made electronically with some documents originally signed. Certain member states require originals and/or certified translations (such as Austria, Poland and Spain).

When the submission is made as an eCTD, the relevant sequence with the marketing authorisation transfer application is sent only to the member state concerned (this is referred to as a "country-specific lifecycle submission"). Subsequent Responses to Questions are also sent only to the member state concerned (CMDh's "Best Practice Guide on the use of the eCTD in the Mutual Recognition and Decentralised procedures" [22]).

For MRP/DCP products it is good practice to send a sequence updated with all the changes submitted in the member states concerned (such as related variations) to the Reference Member States and all the Concerned Member States after finalisation of the transfer and variation procedures.

2.3 Discussion

As we have seen from the review of the marketing authorisation transfer procedure in the EEA member states and the EMA, all the elements checked between the different competent authorities (documents to be submitted, evaluation, timeline and implementation) differed, as expected for a procedure which is handled nationally.

Great differences are found in the documentation to be submitted for the marketing authorisation application (Appendix 3) with the documentation requirements varying widely between member states: from a simple notification with a cover letter and/or a simple form with the minimum required information as in Finland, Germany, Norway and Sweden to extensive documentation which must be annexed, such as for France, Greece, Poland, Romania and the EMA.

Member states that require simple documentation request a cover letter, sometimes accompanied by a simple form, stating the medicinal product(s) concerned and its marketing authorisation number(s) and the date on which the change should take place, together with the basic required attachments (proof-of-establishment, updated product information).

In this case the basic assumption is that no other changes are being notified, apart from the change of marketing authorisation holder to a different legal entity and any additional/consequent changes are submitted separately.

As seen in section 1.2.1, when a marketing authorisation is transferred, nothing should change apart from the information concerning the marketing authorisation holder and the medicinal product will be authorised to the new marketing authorisation holder under exactly the same conditions as previously.

Nevertheless, nearly all competent authorities require declarations providing proof that the new marketing authorisation holder is willing and able to fulfill its obligations (as detailed in Directive 2001/83/EC [1]) to be submitted with the application, such as signed documents from the current and future marketing authorisation holders, respectively waiving and taking over all the rights and responsibilities over the medicinal product concerned (section 2.2.2.1.2).

Declarations stating changes made (such as the QPPV and the pharmacovigilance system) or concerning follow-up measures and special obligations or manufacturer and manufacturing methods or giving assurance that changes will be notified according to the applicable legislation once the transfer is authorised, are sometimes required. Updated information

originally submitted for the marketing authorisation application, such as the person authorised for communication or contact details of the scientific service, is requested to be updated in some member states (Appendix 3).

Templates of declarations, when available, are useful for applicants and competent authorities ensuring valid declarations with the required information included being consistently submitted.

It is also simpler for the applicant to have these declarations placed together in one document signed by the current and proposed marketing authorisation holder as has been done in many of the national application forms (Bulgaria, the Czech Republic, Greece, Ireland, Malta and Slovakia) rather than as separate annexes (as in Romania and for the EMA, where the application includes up to 13 separate annexes).

Another difference in the documentation is the use of an application form or lack thereof and it is important to note the difference in categorisation of the change between member states requiring the use of the EU variation application form (section 2.2.2.1.1).

As a result of the differing requirements, if a medicinal product has to be transferred in several member states, such as for mutual recognition or decentralised procedure products, this can become a considerable administrative burden for the applicant.

Whether a marketing authorisation transfer must be approved or not also differs between member states, although in nearly all member states and for centralised authorised products, approval is required.

As a change may only be implemented after approval, the timeline to approval is of crucial importance in determining when the new marketing authorisation holder may market the medicinal product concerned. For the majority of member states the timeline is between 1 and 2 months but the range extends from immediate implementation with receipt of the application (Austria and Germany) to several months (Finland, the EMA). The differing timelines result in detailed arrangements having to be agreed between the current and proposed marketing authorisation holder regarding the transitional period until all the marketing authorisation concerned are transferred for MRP/DCP products.

The disparities make the planning for submission and implementation of a marketing authorisation transfer rather complicated. Depending on the number of member states involved in a marketing authorisation transfer and which member states, this may be more or less cumbersome and costly.

Factors which have brought about the recent revision of the Variations Regulation and the proposed Clinical Trials Directive revision [23], such as harmonisation and simplification (as part of “Better Regulation” initiatives) could well be applied for marketing authorisation transfers.

3 Changes following a marketing authorisation transfer procedure and their submission

The marketing authorisation transfer procedure concerns a new marketing authorisation holder (legal entity) taking over responsibility for a specific medicinal product resulting in the information concerning the marketing authorisation holder (name and contact details) changing and therefore these are the only changes in the approved dossier and in the product information texts which are a direct result from the marketing authorisation transfer.

However, it is often the case that a marketing authorisation transfer procedure is accompanied/followed by various possible changes.

Below is a list of items which may have to be updated following a marketing authorisation transfer, in the order in which the information is given in the Marketing Authorisation Application Form, if applicable [24]:

- Marketing authorisation number
- Person allowed to communicate with the competent authority on behalf of the applicant
- Name of the medicinal product
- Local representative
- Information on the pharmacovigilance system
- Scientific service
- Manufacturers
- Article 57 database (XEVMPD)

Changes in the following items are outside the scope of the Variation Regulation [5] and are submitted according to the applicable legislation (of the member state concerned or that for centrally authorised products):

- Marketing authorisation number
- Person allowed to communicate with the competent authority on behalf of the applicant
- Local representative
- Scientific service

Changes in the following items are submitted as variations:

- Name of the medicinal product
- Pharmacovigilance system
- Manufacturers

As a result of the amendment of the Variation Regulation, its scope has been extended to include purely-nationally approved products in addition to mutual recognition, decentralised and centralised authorised products as of 4 August 2013 (although the majority of member states had already implemented the Variation Regulation for purely national authorisations before the latest Variation Regulation amendment [25]).
In all cases, the marketing authorisation transfer is submitted according to the national requirements or those for centrally authorised products, as applicable, while variations are submitted separately according to the Variation Regulation, using the EU variation application form [21], regardless of the original authorisation route.

The classification of these specific changes is found in the current Classification Guideline [6]. The updated guidelines will enter into force on 4 August 2013 [26, 27].

This section will describe submissions as will apply after 4 August 2013 only.

3.1 Name of the medicinal product

The name of the medicinal product may be either an invented name, or a common or scientific name (the International Non-Proprietary Name (INN) of the active substance(s) recommended by the World Health Organisation, when available) accompanied by a trade mark or the name of the marketing authorisation holder [15].

A marketing authorisation transfer may therefore result in a change in the name of the medicinal product. This may either be a necessary change because the product name includes the name of the marketing authorisation holder (MAH) as is often the case for generic medicinal products, where the names are often given as “INN MAH”, or because the new marketing authorisation holder would like the product to have a different invented name.

How the change in the name must be notified depends on the procedure by which the product was authorised.

Purely-nationally authorised products

Purely nationally authorised products are authorised in only one member state and have, therefore, one approved invented name.

Notification of a change is submitted as a type IB No. A.2.b variation with the documentation including a completed EU variation application form and amended product information [27].

MRP/DCP authorised products

For products authorised by the mutual recognition procedure (MRP) or decentralised procedure (DCP) it is preferable for the name of a medicinal product to be the same in all the concerned member states [15]. However, as this is not always possible, the medicinal product name may differ in the different member states where the product is authorised.

MRP/DCP authorised products are authorised in more than 2 EEA member states and therefore the product name in the authorised member states may be the same or different.

Depending on the number of member states which are concerned by the marketing authorisation transfer for a MRP/DCP product, the change in the name of the medicinal product may affect one or more member states.

Changes in the name of nationally authorised products are submitted as type IB No. A.2.b variations (documentation: completed variation application form + amended product information) [27].

If the product name in all the member states is identical and the same change is applied for in all member states, the change in product name can be submitted as a single variation.

If the product name in different member states is different, product name changes in more than one member state may be submitted as a grouped variation application (Q.4.8 CMDh's Questions & Answers on Variations [8]).

Some member states request, recommend or allow the submission of the product name application in parallel to the marketing authorisation transfer application (for example when the MAH name is within the product name, Denmark and Italy request it, Spain and Hungary recommend it and Latvia and the Netherlands allow it) (sources: NCA websites (Appendix 6) and [121] for Spain).

Centrally authorised products

For centrally authorised products (CAPs), only one name is acceptable to be authorised in all EEA member states [15] and therefore it is common for CAPs to have an invented name.

For changes in the name of a CAP, the marketing authorisation holder must first apply for a check by the EMA on the acceptability of the new name which may take 4 – 6 months.

Only once the name has been found acceptable, may the marketing authorisation holder change the name of the medicinal product. This change may then be implemented before submission as a variation but must be notified immediately upon implementation to the EMA, as it is classified as a type IAIN variation (immediate notification).

The change is submitted as a type IAIN No. A.2.a variation (documentation: completed variation application form, amended product information and a copy of EMA's letter of acceptance of the new name) [27].

EMA prefers variations to be submitted separately to a marketing authorisation transfer application, even if linked, as is the case when the product name includes the name of the MAH within it. However, in such a case, it is possible to submit the variation at the same time as long as the new name has been found acceptable, though MAHs are advised to contact the EMA Product Team Leader in advance of the submission in order to plan the timeline (Q.15.7 EMA's "Post-authorisation procedural advice for users of the centralised procedure" [4]).

3.2 Pharmacovigilance system

Another change which commonly results from a marketing authorisation transfer is a change in the pharmacovigilance system as each marketing authorisation holder has its own pharmacovigilance system.

Below various elements of the pharmacovigilance system which might be updated are listed:

- Detailed Description of the Pharmacovigilance System (DDPS)
- Summary of the Pharmacovigilance System and Pharmacovigilance System Master File
- Qualified Person for Pharmacovigilance (QPPV)
- Risk Management System

Changes to the description of the pharmacovigilance system

Submission of a variation for a pharmacovigilance system may take the form of:

- replacement of the Detailed Description of the Pharmacovigilance System (DDPS) from that of the current MAH to that of the proposed future MAH (if the marketing authorisation dossier included a DDPS) [28]
- a switch from the DDPS of the current MAH to, or introduction of, a Summary of the Pharmacovigilance System and the Pharmacovigilance System Master File of the proposed future MAH

Replacement of the DDPS from that of the current MAH to that of the proposed future MAH is submitted as a type IAIN C.I.9.d variation if the DDPS has already been assessed by the relevant national competent authority or EMA for a different product [27].

Switch to or introduction of a Summary of the Pharmacovigilance System and the Pharmacovigilance System Master File is submitted as a type IAIN no. C.I.8.a notification [27] which means it is defined as a minor variation which must be notified immediately to the relevant competent authorities but can already be implemented.

Once a medicinal product has a pharmacovigilance system described by the Summary of the Pharmacovigilance System and a Pharmacovigilance System Master File in place, subsequent changes must be submitted as type IAIN no. C.I.8.a notifications [27].

However, once the Article 57 (XEVMPD) database is fully functional, changes to the QPPV and the location of the Pharmacovigilance System Master File will in future not have to be submitted as variations, but the database simply updated [27].

Changes to the Pharmacovigilance System Master File do not require the submission of a variation (section II.A of "Guideline on good pharmacovigilance practices - Module II" [29]) as it is a stand-alone document which is not included in the dossier but the new MAH must ensure that it be kept up-to-date and be permanently available for submission or inspection by the competent authorities [29].

Changes to the Qualified Person for Pharmacovigilance

Each pharmacovigilance system can have only one Qualified Person for Pharmacovigilance (QPPV) and each company (applicant, marketing authorisation holder or group of marketing authorisation holders) must appoint one QPPV responsible for overall pharmacovigilance for all the medicinal products for which the company holds marketing authorisations within the EEA [30].

However, "a QPPV may be employed by more than one marketing authorisation holder, for a shared or for separate pharmacovigilance systems or may fulfil the role of QPPV for more than one pharmacovigilance system of the same marketing authorisation holder" [30].

This means that with a marketing authorisation transfer it is also possible that the new marketing authorisation holder employ the same QPPV.

When this is not the case, the change of QPPV must be notified.

As information concerning the QPPV is a mandatory element of the Pharmacovigilance System Summary, QPPV changes can be included as part of the introduction of a Pharmacovigilance System Summary in one single type IAIN variation (i.e., not as a grouped application of two separate changes), as long as the change is clearly indicated in the present/proposed table of the variation application form (Q. 4.15 of CMDh's Questions & Answers on Variations [8]).

QPPV updates are submitted as type IAIN no. C.I.8.a notifications. However, once the Article 57 database will be fully functional, the QPPV information may be updated directly here without the need to submit a variation [27].

Changes to the Risk Management System

All products applying for a marketing authorisation application since July 2012 must include a Risk Management System, irrespective of the marketing authorisation application legal basis (full or abridged dossier such as generic medicinal products) or procedure (national, MRP, DCP or CP) (Article 8(iaa) of Directive 2001/83/EC, as amended [1]). Previously, only certain applications (such as new marketing authorisation applications for medicinal products which included a new active substance) required its submission.

The Risk Management System is described in the form of an EU Risk Management Plan (RMP) and is submitted as Module 1.8.2.

Any information which has changed which was included in the RMP, such as the the name of the MAH on the cover page of the RMP and the QPPV, is usually included in the next RMP update and no variation must be submitted [31, 32].

3.3 Change to the manufacturers

The marketing authorisation transfer may result in a change of the manufacturer. The change may be the addition of an alternative manufacturer, the deletion of a manufacturer or the replacement of the present manufacturer by a new one, either for the active substance or the finished product.

The type of variation depends on the type of changes involved and on the fulfillment of specified conditions. For example, replacement of a batch release manufacturer is a type IAIN change, deletion of a manufacturing site a type IA and introduction of a new active substance manufacturer supported by an Active Substance Master File a type II [27].

3.4 Grouping and worksharing of variations

When more than one variation is to be submitted (such as a change in the medicinal product name and a switch to the Pharmacovigilance System Summary including a change of the QPPV), it is useful to submit these variations together.

When the same variations affect the same medicinal product these variations may be submitted together in one application as a grouping procedure, as all changes related to a marketing authorisation transfer “in one or more member states … may be grouped in one application according to the highest variation type for the single changes” [33].

When one or more variations affect more than one marketing authorisation from the same marketing authorisation holder and/or authorised via different authorisation procedures (purely national, MRP, DCP, CP) these changes may be submitted in one application via the worksharing procedure (Article 20 of the Variation Regulation) as long as the same change requires no or limited need for additional product-specific assessment [34].

In this procedure there may be different Reference Member States if there are MRP/DCP products involved. In this case one authority (the Reference Authority) examines the application on behalf of the other concerned authorities and is responsible for the validation and evaluation of the application. For MRP/DCP products this Reference Authority is chosen by the Coordination Group (CMDh) from among the member states concerned, taking into account the marketing authorisation holder recommendation [34], while when a centralised authorised product is involved, EMA is the Reference Authority.

Type IA changes may be included in a worksharing procedure as long as type IB or type II variations are also included in the group but line extensions are excluded [34].

Another option available is the "IA-supergroup". This allows the submission of a grouped application of identical (purely administrative or those not affecting the product-specific information) type IA/IAIN variations concerning a group of products from the same MAH with different Reference Member States (RMSs). The application is administered and evaluated by a "lead RMS", suggested by the applicant [35].

However, as this "supergrouping" is complex, it might be better to restrict the submission of a group of type IA variations to MRP/DCP products authorised with the same Reference Member State.

3.5 Article 57 database (XEVMPD) updates

Since July 2012, it is mandatory for each marketing authorisation holder to submit information on its medicinal products authorised in the EEA electronically into a central EMA-managed databank, the Extended EudraVigilance Medicinal Product Dictionary (XEVMPD), as required by Article 57(2), second sub-paragraph of Regulation (EC) No 726/2004, as amended [12] (also called the Article 57 database), irrespective if the product is marketed or not [36].

Mandatory data elements includes those concerning pharmacovigilance, amongst others [37]:

- name of the medicinal product
- marketing authorisation holder
- marketing authorisation number
- QPPV (name, address, contact details)
- contact e-mail and phone number for pharmacovigilance enquiries
- an electronic copy of the latest approved Summary of Product Characteristics

The location of the Pharmacovigilance System Master File data element is not yet mandatory.

Any changes to this mandatory information following a marketing authorisation transfer and subsequent variations have to be updated. However, currently not all functions are active. Once they are, relevant EMA guidance will be published.

3.6 Country-specific requirements

In addition to the above, member states may have country-specific requirements which have to be updated.

For example, in Germany, the *Rote Liste*, the *Fachinfo-Service* and IFA must be updated, where appropriate.

The *Rote Liste* is a listing of authorised medicinal products used by healthcare professionals [38], the *Fachinfo-Service* is a compendium of the Summary of Product Characteristics for medicinal products authorised in Germany accessed by healthcare professionals only [39] and IFA (*Informationsstelle für Arzneispezialitäten GmbH*) is the registration agency responsible for the German pharmaceutical central numbering system, whereby each product is assigned a *Pharmazentralnummer* (PZN) used for reimbursement in the public health system [40].

3.7 Summary

The marketing authorisation transfer is submitted for each product separately in the member state concerned as a purely national application.

Changes within the scope of the Variation Regulation are submitted as variations, while those outside the scope are submitted according to local requirements, except for Article 57 database changes that apply throughout the EEA regardless of the procedure by which the medicinal product was authorised.

4 Submission of post marketing authorisation transfer regulatory activities – current situation

In this section the current situation concerning the submission of regulatory activities which may have to be submitted as a result of a marketing authorisation transfer will be described.

4.1 Timing of submission of changes related to the marketing authorisation transfer

As seen in the previous section (section 3), regulatory activities related to the marketing authorisation transfer vary in how they have to be submitted. Some are submitted according to local legislation, some according to the Variation Regulation.

Even if specific national competent authorities consider certain variations as being consequent: a change that is "unavoidable and direct result of another change (i.e. the 'main change') and not simply a change which occurs at the same time" (EMA definition - Q. 5.2 from "Post-authorisation procedural advice for users of the centralised procedure" [4]) to the marketing authorisation transfer, as the marketing authorisation transfer is not within the scope of the Variation Regulation, the marketing authorisation transfer application must be submitted separately from the changes.

There are different possibilities regarding when the changes related to the marketing authorisation transfer should be submitted (before, during or after the marketing authorisation transfer).

Related changes are usually submitted after the marketing authorisation transfer application has been submitted by the new marketing authorisation holder.

However, by mutual agreement between the current and future marketing authorisation holders, these changes may also be notified/submitted before the marketing authorisation transfer takes place (such as a change of the pharmacovigilance system).

This must be carefully considered as some competent authorities request marketing authorisation transfer applications not to be submitted with on-going procedures (such as variations, renewals or Periodic Safety Update Report (PSUR) applications) and to submit variations only once the transfer procedure has ended (been approved). This is the case for the Netherlands, the United Kingdom and the EMA [148, 166, 4].

Some competent authorities (such as Romania) will assess related variations only once the marketing authorisation transfer is finalised (approved) [81].

Changes may also be submitted in parallel to the marketing authorisation transfer application. This is possible for certain common related changes such as a product name change or a

change in the pharmacovigilance system in specific competent authorities or when this has been previously agreed with the competent authority concerned (for purely nationally authorised products) or the Reference Member State (for MRP/DCP).

This is especially important in mutual recognition and decentralised procedures because of the different timelines of the marketing authorisation transfer in different member states. The marketing authorisation holder should contact the Reference Member State (RMS) before the transfer and discuss the timing of the submission of the related changes: it may then be possible to submit the changes to the RMS and all the concerned member states at the same time, such as after submission of all the transfer applications to the member states concerned but before approval.

Being the coordinator of all procedures [42] and acting as a regulatory advisor to the applicant, the RMS can help the applicant find a solution acceptable to all parties (the RMS as the scientific assessor of the documentation, the Concerned Member States and the marketing authorisation holder) [43].

The RMS will consider the request case-by-case depending on various factors such as the number and type of changes.

In conclusion, the timing of the submission of related changes must be checked case-by-case, depending on the competent authority/ies and the change(s) concerned.

4.2 Examples

A few examples of various marketing authorisation transfer applications and the associated submission of variations are discussed below.

Case 1

The simplest case is a marketing authorisation transfer which concerns one medicinal product authorised to one marketing authorisation holder by one competent authority (i.e., a product authorised via a purely national or centralised procedure).

The marketing authorisation transfer is submitted to the competent authority concerned according to the applicable legislation.

This may be relatively simple (as in Germany or Finland) or more complicated (as for Poland, Romania or the EMA) in terms of the documentation to be submitted (section 2.2.2).

If there is more than one variation to be submitted, the option of grouping the changes in one application may be used (section 3.4).

Although different member states define marketing authorisations differently (see section 1.2.3), for variation notifications/submissions marketing authorisations are defined as "all strengths and/or pharmaceutical forms of a certain product" (Q. 1.4 of CMDh's Questions & Answers on Variations [8]) and therefore all strengths and/or pharmaceutical forms of a product may be included in the same single variation application.

Case 2

Another possibility is a medicinal product authorised via MRP or DCP which is therefore authorised in two or more member states.

The transfer of the marketing authorisation may apply only to one member state or to more, as another company may buy the product in one or more specific member states or in all the member states.

The marketing authorisation transfer is submitted to the member state(s) concerned as a national application, informing the Reference Member State of the change [8].

Depending on the number of member states involved and which member states, preparation of the documents to be submitted may be more or less cumbersome as each member state has its own requirements, ranging from the simple to the relatively complicated (section 2.2.2).

As before, grouping of the variations is possible, as even if a MRP/DCP product belongs to different MAHs, for the purposes of submission of variations in grouping and worksharing they can be considered as "the same MAH" (Q. 4.2 of CMDh's Questions & Answers on Variations [8]).

However, even if the variations affect only a specific member state, for MRP/DCP products the variations must be submitted to all the member states (the Reference Member State and all the Concerned Member States) where the product is authorised (Qs. 2.2 and 2.8 of CMDh's Questions & Answers on Variations [8]).

As seen before, if several member states are involved, it is recommended for the applicant to discuss the timing of the submission of the marketing authorisation transfer and related changes with the RMS in advance, in order to be able to submit all the variations together.

As a MRP/DCP product may have different MAHs in the member states were it is authorised, coordination between all the MAHs to which the specific medicinal product is authorised is imperative in order to maintain the dossier (including product information texts) harmonised throughout the product's lifetime, including submission of variations and renewal applications and the monitoring of the product's safety (pharmacovigilance).

Case 3

In the case of a company merging with another or being taken over by another, the full portfolio of the company is transferred to the new company. This means that all its authorised products must be transferred to the new marketing authorisation holder.

This is the most complex example, as the number of products involved may be large and the procedures by which they were authorised may differ (purely national, MRP, DCP, CP).

The products must be transferred to the new marketing authorisation holder in independent applications in the member states concerned. This must be done for each product separately, unless grouping of marketing authorisation transfer applications in the member state concerned is possible.

For MRP/DCP products, the Reference Member State(s) must be informed of the marketing authorisation holder change of medicinal product(s) in the member state(s) concerned.

For a more efficient and timely submission of a large number of variations it is recommended to discuss their submission with the various Reference Member States in advance. For centrally-authorised products, EMA advices consultation with the Product Team leader at least one month before submission of the marketing authorisation transfer [4].

A possibility for submission of the variations is to use the worksharing procedure, when the same change (which must require no or limited need for additional product-specific assessment) is submitted for different marketing authorisations (which may have been authorised via different routes) in the same application. An example would be the introduction of a summary of the pharmacovigilance system for a new MAH for many different products after marketing authorisation transfers following a merger.

This option must be carefully considered, however, because of the complexity of handling a procedure where a number of different products are involved.

Up to now, worksharing has not been used very much by industry (74 MRP/DCP worksharing procedures were started in 2012 [44]), as its complexity requires proper planning, it must be requested at least 6 weeks before submission and assessment takes 60 days (as for type II variations) [34]. Its great advantage is that the application is assessed by one Reference Authority and therefore one opinion (result) is obtained.

4.3 Discussion

The number of scenarios of a marketing authorisation transfer are many. The situation becomes increasingly complex the more medicinal products / member states / procedures are involved in the marketing authorisation transfer for which variations must be submitted.

For complex examples, submission of the marketing authorisation transfers and related variations should be well planned in advance and preferably cordinated with the relevant competent authority, such as the reference member state(s) for MRP/DCP or the EMA for centrally authorised products, before submission.

A thorough understanding of the Variation Regulation and associated guidance documents (Classification Guideline, Best Practice Guides, EMA and CMDh procedural guidance) (see section 1.1) and of the myriad possibilities for grouping and worksharing is of crucial importance in order for the marketing authorisation holder to submit the most appropriate variation submission for the case in question.

If the changes include updates to the product information texts (such as changes to the marketing authorisation number, local representative, product name and/or manufacturers) the regulatory activities should be well-planned in order to avoid repeated submissions which affect the texts.

In the next section, the advantages and disadvantages of the current EU marketing authorisation transfer procedure will be discussed.

5 Advantages and disadvantages of the current marketing authorisation transfer system

The current marketing authorisation transfer procedure is handled as a purely national procedure, regardless of the original authorisation route of the product. Any subsequent variations are submitted separately according to the Variation Regulation.

In this section, the advantages and disadvantages of the current marketing authorisation transfer system will be discussed.

5.1 Advantages of the current marketing authorisation transfer system

As the current marketing authorisation transfer procedure is a purely national procedure, it is only submitted in the competent authority concerned: for purely nationally authorised and MRP/DCP authorised products the competent authority(s) concerned and EMA for centrally authorised products.

As a consequence, if a MRP/DCP product is transferred to another company, unlike variations, which must be submitted to all the member states involved in the MRP/DCP, even if they are not concerned by the change, the marketing authorisation transfer is submitted only in the member state(s) concerned, i.e., in the member state where a change of marketing authorisation holder (legal entity) is applied for.

The submission of the marketing authorisation transfer only in the member state(s) concerned, therefore, saves the marketing authorisation holder time, planning and fees which would be associated with submission in the member state(s) not concerned by this change.

This means that the marketing authorisation transfer of a product is relatively simple, depending on the requirements of the member state concerned, especially if the marketing authorisation transfer concerns one product only authorised in only one or in a small number of MRP/DCP member states.

5.2 Disadvantages of the current marketing authorisation transfer system

Being a purely national procedure, the requirements and timeline differ from member state to member state, resulting in greatly differing systems (section 2.2). The applicant must first obtain information concerning the marketing authorisation transfer requirements, not always available in English from the national competent authority website.

If an applicant has to submit a marketing authorisation transfer application in several member states, be it different products with purely national marketing authorisations authorised in different member states or a MRP/DCP product, the requirements vary between the member

states. For each member state, the marketing authorisation transfer application must be prepared, taking into account the country-specific requirements, documents and fees, which is more time-consuming and expensive than would be preparing the same documentation for several member states.

When the marketing authorisation transfer is a result of a company merger or takeover and all the products must be transferred, this becomes a very complex and costly procedure.

In addition, the possibility of grouping marketing authorisation transfer applications, which is useful when many products are to be transferred (after a merger or acquisition) is only possible in a minority of competent authorities (such as Austria under certain conditions [89] and Norway [78]).

A marketing authorisation holder transfer is often accompanied by other changes. Changes which are submitted in accordance with the Variation Regulation are usually submitted after the marketing authorisation transfer. As the marketing authorisation transfer procedure has different timelines in different member states, this results in the submission of these changes having to be submitted in each member state separately, rather than being able to take full advantage of all the grouping and worksharing possibilities available in the Variation Regulation. This means that when several member states are involved (a MRP/DCP product involving several member states or the transfer of several products in different member states) the submission of these variations requires a lot of planning and the new marketing authorisation holder has to keep careful tracking of the outcome of the marketing authorisation transfer in the different member states in order to submit the subsequent variations.

Differing timelines also means that implementation (marketing the transferred product under the new marketing authorisation holder's responsibility and with the revised product information) is only possible at different times for different member states, requiring further coordination from the marketing authorisation holder.

Only if the Reference Member State of the MRP or DCP authorised product is prepared to be flexible and the applicant has made the request in advance, a timeline may be agreed to overcome this problem, such as after the submission of the marketing authorisation transfer application in all the member states concerned.

Another disadvantage of the current system is that for some competent authorities the contact person for the marketing authorisation transfer is the current MAH (e.g., Bulgaria, the

Netherlands, the EMA), while for others it is the future MAH (Austria, Spain, the UK) (sources: NCA websites (Appendix 6), [4] for EMA and [119] for Spain).

This means that any questions during the procedure or notification of approval required for implementation may be sent to the current or future MAH, depending on the member state concerned, which makes management of the procedure when several member states are involved, such as in MRP/DCP products, more complicated.

5.3 Conclusion

Although for specific member states the current marketing authorisation transfer is relatively simple, the differing requirements between member states may make a marketing authorisation transfer submission involving several member states logistically quite complicated.

6 Proposal for a possible future marketing authorisation transfer system

In this section, two hypothetical marketing authorisation transfer systems will be discussed: the inclusion of the marketing authorisation transfer in the Variation Regulation and a EEA-wide marketing authorisation transfer similar to the current Article 61(3) system.

6.1 Inclusion of the marketing authorisation transfer in the Variation Regulation

Currently, a change of marketing authorisation holder where it remains the same legal entity is within the scope of the Variation Regulation [5] and is listed in the Classification Guideline [6].

A change of marketing authorisation holder involving a change of the legal entity could be included below it in the Variation Classification Guideline (changes marked in red).

Administrative change:

A.1 Change in the name and/or address of the marketing authorisation holder	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The proposed marketing authorisation holder remains the same legal entity.	1	1, 2	IA_{IN}
b) The proposed marketing authorisation holder is a different legal entity.	2,3,4	1, 2	x
Conditions			
1. The marketing authorisation holder shall remain the same legal entity.			
2. The proposed marketing authorisation holder is a different legal entity.			
3. The proposed marketing authorisation holder has a Pharmacovigilance System in place and a QPPV at its disposal.			
4. No changes in the dossier or product information are made, apart from name and contact details of the marketing authorisation holder.			
Documentation			
1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.			
2. Revised product information.			

6.1.1 Classification of the marketing authorisation transfer change – a future model?

A decision would have to be made on the classification of this variation and the documentation required for this change, based on the experience of national competent authorities with varying classification and requirements, on feedback from stakeholders (competent authorities and industry) and possibly impact assessment.

The classification of a change is based on level of risk to public health and the impact it has on the quality, safety or efficacy of the medicinal product. If there is no impact or it is minimal, the change is classified as minor (type IA and type IB), while a major change (type II) may have a significant impact on the quality, safety or efficacy of the medicinal product [5].

The evaluation procedure is adapted accordingly: type IA changes do not require approval and can be implemented before notification (but type IAIN changes must be notified immediately after implementation while type IA changes must be notified within a year from implementation), type IB may be implemented if no objections are received after 30 days and type II changes must be approved before implementation [5].

Variation applications for purely nationally authorised products are submitted only in the member state concerned while the EMA evaluates centrally authorised products' variations.

For MRP/DCP products, submission must always be done in the Reference Member State and all the Concerned Member State(s) and the involvement of the Concerned Member State(s) varies according to the variation type: for type IA, only the Reference Member State decides on the validity of the variation while for type IB and type II the Reference Member State may consult a Concerned Member State. For type II variations the Concerned Member State(s) may raise objections based on potential serious risk to public health grounds [7].

Currently, categorisation of the marketing authorisation transfer change ranges from a change which does not require approval (a type of self-certification by the applicant) (Table 4) to a classification as a type II change (Table 2). The timeline of the marketing authorisation transfer is decided by each national competent authority. For member states which have categorised the marketing authorisation transfer change as a specific variation type, the timeline does not necessarily follow that of the Variation Regulation.

Despite the disparity in classification and timeline, a choice of type IB might be a good compromise between the differing national competent authority categorisation choices, allowing the member state(s) concerned by the marketing authorisation transfer to provide input for MRP/DCP products (submission of a change for a purely nationally authorised

products is made only in the member state concerned) and the marketing authorisation holder to implement the change 30 days after validation.

6.1.2 Advantages of inclusion of marketing authorisation transfer in the Variation Regulation

The inclusion of a marketing authorisation transfer within the scope of the Variation Regulation would make the preparation of a marketing authorisation transfer application easier in that all the information required by the applicant to prepare the application would be found in one source (the Classification Guideline) and the same documents (such as the same EU variation application form) would be required, regardless of the member state.

Any additional country-specific requirements could still be added as is currently the case. These are listed in the CMDh document "Data requested for variations … in the MRP/DCP" [45].

Planning for implementation would be easier as all the member states would have the same timeline. This would be especially useful in products where the marketing authorisation transfer takes place in several member states.

Inclusion of the marketing authorisation transfer in the Variation Regulation would also allow for the possibility of grouping and worksharing of changes: several marketing authorisation transfers could be grouped together, even if different products are involved and a marketing authorisation transfer could be grouped with any additional variations associated with the transfer.

Changes which affect the product information texts, such as the marketing authorisation transfer and product name change, could all be assessed in parallel, producing one updated product information version, rather than several subsequent ones with each change affecting the texts. In addition, changes associated with a marketing authorisation transfer which are not within the Variation Regulation (such as a change of the local representative) which affect the product information texts could be included and tracked, rather than having to submit as a separate Article 61(3) application, as recommended by the CMDh [46] and be easily documented in the "present / proposed" table of the variation application form.

In addition, the use of the EU variation application form could be supplemented by a standard cover letter to be used for marketing authorisation transfer submissions similar to the template for the cover letter used in MRP/DCP variation applications [47] where additional declarations from the current and proposed marketing authorisation holder concerning rights and obligations could be included.

6.1.3 Disadvantages of inclusion of marketing authorisation transfer in the Variation Regulation

Inclusion of the marketing authorisation transfer within the scope of the Variation Regulation would require a change in legislation.

Currently each member state concerned deals with its national marketing authorisation change. Inclusion in the Variation Regulation would result in additional workload for specific Competent Authorities which are significantly more popular as Reference Member States for MRP/DCP than others. In 2012 these were Germany, the Netherlands, Portugal and the United Kingdom [44].

From the point of view of the applicant, inclusion in the Variation Regulation would mean that a change of marketing authorisation holder would have to be notified to all the competent authorities in a MRP/DCP procedure, even if not directly concerned. This would mean preparation for submission in all the competent authorities and the payment of fees, for a change which does not affect that specific member state and does not evaluate it.

However, submission of the marketing authorisation transfer to all member states is not that time-consuming if the marketing authorisation holder takes advantage of the Common European Submission Platform (CESP). Currently, 19 out of 30 EEA member states are participating [48]. Submission via this portal replaces electronic submission for purely nationally authorised and MRP/DCP products with electronic media (CD / DVD), saving time (burning the information on the CD, running the technical validation) and money (sending the CD to each member state with a courier service). The EMA has its own portal, the eSubmission Gateway, and is currently not participating in CESP because of limited resources [49].

Concerning fees, a specific fee structure could be chosen for marketing authorisation transfers where a fee would be paid only in the Reference Member State and the Concerned Member State(s) involved, as changes related to the marketing authorisation transfer have to be submitted to all the member states concerned for MRP/DCP products, even if they affect only one (section 4.2 Case 2). Maybe this could be taken into consideration in the fee structure, as has been commented by the European Generic Medicines Association [50].

6.1.4 Inclusion of marketing authorisation transfer in the Variation Regulation – conclusion

Inclusion of a change of marketing authorisation holder where there is a change of legal entity in the Variation Regulation would allow harmonisation of requirements, timelines and implementation. Although there would be disadvantages for the marketing authorisation holder (mainly concerning the fees and submission to all the member states for MRP/DCP products even if not concerned by the change) there would also be advantages, especially in the preparation for submission when several member states are involved in that the same documentation has to be prepared for all and in the possibility of grouping. This grouping would be useful both for the applicant and for the authority overseeing the change.

Although a marketing authorisation transfer affects only the member state where the change of marketing authorisation holder takes place, a few purely national changes are already included in the Variation Regulation and the Variation Classification Guideline, such as a change of the name/address of the marketing authorisation holder when it remains the same legal entity (variation no. A.1), change of the product name (variation no. A.2) and a change in pack size of the finished product (variation no. B.II.e.5) [6].

The change would probably also affect different sized companies differently: small companies with a small number of products might find this system more of an adminstrative and financial burden than global players, where the advantages of harmonisation for a great number of member states might be of great benefit.

6.2 EEA-wide marketing authorisation transfer procedure

Another possibility could be the establishment of a marketing authorisation transfer procedure applicable for all submissions (national, MRP, DCP, centralised).

As an example, current CMDh guidance for the Article 61(3) procedure of Directive 2001/83/EC could be taken.

The Article 61(3) procedure is an application for submission of minor changes to the labelling or package leaflet not affecting the Summary of Product Characteristics, such as change in user or storage instructions or the expression of side effects or for European (i.e., not purely national, such as translation issues or Blue-box information) aspects of the label and package leaflet where a harmonised position has previously been reached and is to be maintained.

This procedure, like the marketing authorisation transfer, is outside the scope of the Variation Regulation and is therefore applied nationally for purely nationally authorised products. Purely nationally authorised products are submitted to the member state concerned, MRP/DCP products to the Reference Member State and all Concerned Member States and centrally-authorised products (CAPs) to the EMA.

However, unlike the marketing authorisation transfer, information is available for MRP/DCP products in the CMDh website [51]. For CAPs, guidance is available in the EMA website [4]. The guidance includes details on the timeline and the evaluation procedure and for MRP/DCP, a cover letter template and a notification form.

For purely nationally authorised products, each national competent authority website must be searched to be checked for information concerning Article 61(3) submissions, as the procedure varies from member state to member state. Some have a national Article 61(3) notification form (as in Ireland, Sweden and the United Kingdom) and the timeline and evaluation may vary. For example, in the United Kingdom this notification is a self-certifying procedure.

The Article 61(3) procedure is meant to be used for simple changes. According to the CMDh the timeline is therefore short (20 days) but may, in exceptional cases where amendments are required, continue up to 90 days [46]. For CAPs, the EMA notification is issued within 90 days if the changes are acceptable.

Similarly to what is currently available for the Article 61(3) procedure for MRP/DCP, guidance could be provided for marketing authorisation transfers stating common requirements, a template cover letter and a standard application form.

The timeline, evaluation procedure (as currently the range from self-certification to formal approval exists in the member states) and possibly a fee scheme (would the fee be the same in member states which are not directly concerned by the change?) would have to be discussed and agreed upon.

6.2.1 Marketing authorisation transfer EEA-wide procedure - advantages

The advantages of a EEA-wide procedure would be that requirements and timelines could be harmonised for MRP/DCP products, making preparation of a submission (standard cover letter and application form with the required documentation for all member states) and post-marketing authorisation transfer activities planning easier for the applicants.

6.2.2 Marketing authorisation transfer EEA-wide procedure – disadvantages

To reach the harmonisation required would require the agreement of all the stakeholders (national competent authorities, EMA and industry) concerning requirements and timelines.

As with the current system, submission of subsequent variations would have to be made separately under the Variation Regulation.

6.2.3 Marketing authorisation transfer EEA-wide procedure – conclusion

Establishment of a specific EEA-wide marketing authorisation transfer procedure would probably be more difficult and time-consuming than the alternative of inclusion in the Variation Regulation.

7 Conclusion

From the review of the current procedures for marketing authorisation transfer of human medicinal products in the EEA it is clear that the marketing authorisation transfer procedure varies a lot depending on the member state concerned.

This lack of harmonisation causes various difficulties for the applicants in the preparation of the marketing authorisation transfer submission and the planning of activities associated with the transfer, such as the submission of other changes which may result from it, especially if different member states are involved as in a MRP/DCP or the procedure must be submitted for many products after a merger or acquisition of a company.

In the European Commission public consultation paper from 2011 on the review of the Variations Regulation [52], it was said regarding changes that “Changes affecting purely national authorisations are handled according to national rules, which can vary among member states. From a public health perspective, this disharmonised situation does not appear justified”.

According to the 2008 Commission proposal for amendments of legislation regarding variations [53], (the amendment) “… would ensure that all medicinal products, regardless of the procedure under which they have been authorised, are subject to the same criteria for the evaluation, approval and administrative treatment... “ as part of a 'Better Regulation' initiative “to make the framework simpler, clearer and more flexible, without compromising public and animal health” and that “From a legal perspective, it does not seem justified that the requirements for the granting of the initial marketing authorisation are fully harmonised at Community level, whereas the post-authorisation requirements are not.”.

It would therefore be worthwhile to rethink a change in the way marketing authorisation transfers are handled in line with the European Union policy of harmonisation (such as the latest Variation Regulation amendment extending its scope to purely nationally authorised products), rationalisation and transparency (easily available information regarding requirements, the review process, implementation).

A possibility that has been discussed in this thesis is instituting a EEA-wide procedure, such as under the Variation Regulation, based on the experience of member states where simple procedures have had no negative impact on the safety and quality of the medicinal products.

If a harmonised system has been achieved for the marketing authorisation application and variation procedures, it should be possible to achieve a unified system for marketing authorisation transfer as well, while maintaining the same level of public health protection.

However, with the great number of current regulatory legislative changes (new pharmacovigilance requirements, amended Variation Regulation) resulting in an increased workload both for the competent authorities and the marketing authorisation holders, it is unlikely that changing the marketing authorisation transfer system will be a priority soon.

A more unified marketing authorisation transfer system would make a smooth transition of a product from one marketing authorisation holder to another easier, ensuring a continuous supply of the product on the market, which is important in terms of public health and of course, of interest to the competent authorities and, commercially, to the new marketing authorisation holder.

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48. CMDh's "Requirements on eSubmissions (NeeS and eCTD) and paper documentation for Variations and Renewals within MRP or National procedures" CMDh/006/2008/Rev.7 (March 2013) http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/eSubmissions/CMDh_006_2008_Rev7_2013_03.pdf

49. Q.2 – General questions – FAQs – Common European Submission Platform http://cesp.hma.eu/FAQs

50. European Generic Medicines Association's Position Paper "Submission of comments on "Guideline on the details of the various categories of variations""15 July 2012 http://ec.europa.eu/health/files/betterreg/pc_result_var_2013/14_ega.pdf

51. CMDh Article 61(3) guidance http://www.hma.eu/101.html

52. European Commission Health and Consumers Directorate-General "Review of Commission Reg (EC) No 1234/2008" Brussels, Public consultation paper (21/09/2011) http://ec.europa.eu/health/files/betterreg/2011_09_21_public_consultation.pdf

53. Commission “Proposal for a directive of the European Parlamient and of the Council amending Directive 2001/82/EC and Directive 2001/83/EC as regards variations to the terms of marketing authorisations for medicinal products” (04.03.2008)
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0123:FIN:en:PDF

54. Abbreviations for countries from Europa’s “Interinstitutional Style Guide” (updated 01.07.2013)
http://publications.europa.eu/code/en/en-370100.htm

55. Head of Medicines Agencies -contact points:
http://www.hma.eu/index.php?id=66

References 56. – 86. are found in Appendix 5 (IDRAC references) and 87. – 169. in Appendix 6 (national competent authorities’ sources of information)

Appendix 1 EEA member states two-letter abbreviations and competent authorities

	Abbreviation [54]	Member State	Competent Authority [55]
1	AT	Austria	Austrian Medicines and Medical Devices Agency
2	BE	Belgium	Federal Agency for Medicines and Health Products
3	BG	Bulgaria	Bulgarian Drug Agency
4	CY	Cyprus	Ministry of Health
5	CZ	Czech Republic	State Institute for Drug Control
6	DE	Germany	Federal Institute for Drugs and Medical Devices (*Bundesinstituts für Arzneimittel und Medizinprodukte - BfArM*)
7			Paul Ehrlich Institute (PEI)
8	DK	Denmark	Danish Health and Medicines Authority (DMA)
9	EE	Estonia	State Agency of Medicines
10	EL	Greece	National Organization for Medicines
11	ES	Spain	Agencia Española del Medicamento y Productos Sanitarios (AEMPS)
12	FI	Finland	Finnish Medicines Agency (FIMEA)
13	FR	France	French National Agency for Medicines and Health Products Safety (*Agence nationale de sécurité du médicament et des produits de santé* – ANSM)
14	HU	Hungary	National Institute for Quality- and Organizational Development in Healthcare and Medicines
15	IE	Ireland	Irish Medicines Board
16	IS	Iceland	Icelandic Medicine Agency
17	IT	Italy	Italian Medicines Agency (*Agenzia Italiana del Farmaco* - AIFA)
18	LI	Liechtenstein	*Amt für Gesundheit*
19	LT	Lithuania	State Medicines Control Agency
20	LU	Luxembourg	*Direction de La Santé*
21	LV	Latvia	State Agency of Medicines (SAM)
22	MT	Malta	Medicines Authority
23	NL	The Netherlands	Medicines Evaluation Board (MEB)
24	NO	Norway	Norwegian Medicines Agency
25	PL	Poland	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
26	PT	Portugal	National Authority of Medicines and Health Products (*Instituto Nacional da Farmácia e do Medicamento* - INFARMED)
27	RO	Romania	National Agency for Medicines and Medical Devices
28	SE	Sweden	Medical Products Agency (MPA)
29	SI	Slovenia	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
30	SK	Slovakia	State Institute for Drug Control
31	UK	United Kingdom	Medicines and Healthcare products Regulatory Agency (MHRA)

Appendix 2 Legal basis for the marketing authorisation transfer

	EEA member state	Legal basis for the marketing authorisation transfer
1	AT	§ 25 of the Austrian Drug Law (*Arzneimittelgesetz* (AMG)) (BGBI. No. 185/1983 as amended) [56]
2	BE	Article 34 §1 of the Royal Decree dated 14.12.2006 [57]
3	BG	Ordinance No. 27 of 15.06.2007, as amended [58]
4	CY	- [100]
5	CZ	Law 378/2007 Coll.on pharmaceuticals (§ 36) and the Decree 228/2008 Coll. [60]
6	DE-BfArM	Change not subject to approval (*Nicht zustimmungspflichtige Änderungsanzeige*) acc. to § 29 Abs. 1 AMG (*Arzneimittelgesetz* = German Drug Law) [61]
7	DE-PEI	
8	DK	*Information not available*
9	EE	Estonian Medicinal Product Act §77 (3) (RT I 2005, 2, 4) [63]
10	EL	Circular Letters of National Organization of Medicines with ref. nos. 55107/4-8-10, 38889/11-6-08 and 68962/22-10-2007 [64]
11	ES	Royal Decree 1345/2007 of 11 October 2007, as amended by Royal Decree 1091/2010 of 3 Sept. 2010 and AEMPS Information Note MUH/13/2012 (Processing of MA transfer applications for pending MA applications) of 2 August 2012 [65]
12	FI	Fimea Administrative regulation 1/2009, sections 8.3.2 and 8.4 [124]
13	FR	Article R.5121-46 of the Public Health Code (*Code la Santé Publique* (CSP)) [67]
14	HU	Section 5(9) of Act XCV of 2005 (Hungarian Medicines Act) [68]
15	IE	MA transfer guideline "IMB Guide to Transfers of Marketing Authorisations, Parallel Import Licences and Dual Park Import Registrations for Human Medicines" - AUT-G0019-6 (17.11.2011) [134]
16	IS	*Information not available*
17	IT	Ministerial Circular 9 of 18 July 1997 [71]
18	LT	Law on Pharmacy No X-709 of 22 June 2006, Decree No. V-596 of 15-Jul-2007 and related amendment (Decree V-209 of 11 March 2011) [73]
19	LU	*Information not available*
20	LV	The Cabinet of Minister's Regulations No.376 Medicinal Product Registration Procedure of 9 May 2006 [75]
21	MT	- [147]
22	NL	*Information not available*
23	NO	*Information not available*

	EEA member state	Legal basis for the marketing authorisation transfer
24	PL	MA transfer procedure: art. 32 of the Polish Pharmaceutical Law [79]
25	PT	Article 37 of Decree-Law No. 176/2006 as amended by Decree-Law 20/2013 [80]
26	RO	Order of the Minister of Public Health no 1206 of 2.10.2006 (Approval of Norms relating to examination of an application for the transfer of a MA), NMMDA Scientific Council Decision No. 36 of 15.12.2000 (Approval of Regulations Regarding the Evaluation of the Requests for Transfer of MA) [81]
27	SE	Swedish provisions LVFS 2006:11 as amended [82]
28	SI	Article 53 of the Drug Law 31/2006 of 24 March 2006 and Chapter V, articles 52 and 53 of "Regulations: Procedures Relevant to the Marketing Authorization of Medicinal Products for Human Use" of 30 December 2010 (Official Gazette of the Republic of Slovenia, No. 109/10) [83, 158]
29	SK	Law 244/2012 of 13 September 2011 amending Law 362/2011 on Medicinal Products and Medical Devices (the Drug Law) [84]
30	UK	No legal basis – considered an administrative procedure. [167]

Appendix 3 Table of main marketing authorisation transfer documentation requirements for authorised products

See end of table for list of abbreviations

	CA	AF	Current MAH's waiver of responsibility for MP	Proposed MAH's ability to take over responsibility	Other
1	**AT**	2 national AFs: MA transfer AF + national changes AF (in German only) [88]	Waiver declaration from current MAH [87] (original) [56]	- Declaration of proposed MAH that complete dossier has been provided [87, 88] (original) [56] - Declaration of proposed MAH that will take over all rights & responsibilities [87, 88] (original) [56] - Proof of PVS of future MAH [MA transfer AF]	Declaration no change of manufacturer [MA transfer AF]
2	**BE**	EU-VAF (type IA) [90]	Transfer agreement (current MAH transfers rights & obligations for MP, proposed MAH accepts these, complete dossier made available, effective date) signed by current and future MAH (pdf) [91, 93]		Additional requirements (such as copy of the manufacturing authorisation, translations) [91, 92, 93]
3	**BG**	National MA transfer AF (in Bulgarian and English) [58]	Declaration from current MAH that access to complete updated dossier given to future MAH (Annex 2 of AF).	- Declaration of proposed MAH (access been provided and will take over all rights & responsibilities on effective date) (Annex 1 of AF). - Contact details of QPPV information in AF + CV - Contact details of scientific service in AF	Additional requirements (such as certified POAs) [58]

	CA	AF	Current MAH's waiver of responsibility for MP	Proposed MAH's ability to take over responsibility	Other
4	**CY**	EU-VAF (type II) [96, 98]	Declaration access been provided & will transfer all rights & responsibilty on effective date (see proposed MAH documents) [96]	[96]: - Availability of complete dossier statement (by current / proposed MAH) - Proposed MAH statement concerning ability to take over MP from the effective date - Copy of the agreement between the two MAHs for the transfer of the MA and the approval of the manufacturer for this transfer. - Contact details of QPPV information + CV - Contact details of scientific service - Contact details of local representative (*if applicable*)	- Proposed MAH is in possession of the original MA (statement by current / proposed MAH) [96] - Additional requirements (such as Wholesale License (*if applicable*), size & organisation of the proposed MAH, details on manufacturer(s) and its sites) [96]
5	**CZ**	National MA transfer AF (in Czech and English) [102]	Declaration access to full dossier been provided to proposed MAH (Annex 2 to AF) [102]	- Availability of complete dossier statement and agrees to transfer from the effective date (proposed MAH) (Annex 1 to AF) [102] - Contact details of QPPV information in AF + CV - Contact details of scientific service in AF	PoAs for current and proposed MAH [102]

	CA	AF	Current MAH's waiver of responsibility for MP	Proposed MAH's ability to take over responsibility	Other
6	**DE**	BfArM notification form (available in English) [109]	-	-	-
		PEI notification form for a notification not subject to approval (*nicht zustimmungspflich-tige Änderungsanzeige*) (only in German) [112]	-	-	-
7	**DK**	EU-VAF (type IB) [114]	Transfer declaration (current MAH transfers rights & obligations for MP, proposed MAH accepts these, complete dossier made available, effective date) [114, 62]		-
8	**EE**	EU-VAF (type II) [63]	Confirmation of transfer of MA from previous MAH (may be together with *) [63]	[63]: - Confirmation for taking over the responsibilities from new MAH (*) - Document identifying QPPV + CV + contact details (address, e-mail, tel. and fax nos.)	- Originally signed POA for person authorised for communication for new MAH [63]

	CA	AF	Current MAH's waiver of responsibility for MP	Proposed MAH's ability to take over responsibility	Other
9	**EL**	National MA transfer AF (in Greek and English) [64]	Access to full dossier provided to proposed MAH and will continue to be responsible for products marketed under its name (declaration in AF) [64]	[64]: - Availability of complete dossier, agrees to take over all rights & responsibilities (proposed MAH) (declaration in AF) - Submission of PVS and RMS (*if applicable*) or proof already submitted - Contact details of QPPV info. + CV - Contact details of scientific service - Contact details of person in charge of complaints - Declaration if any FUM & SOs and if so, listing them (signed by proposed MAH)	[64]: - Copy of the MA - Additional rqmnts. (such as PoA (concerning proposed MAH company), declaration if product not yet marketed)
10	**ES**	EU-VAF (in Spanish only) (type II) [120, 121]	- Transfer declaration between current and proposed MAH (see #) [120]	[120]: - Transfer declaration between current and proposed MAH (legalisation by Hague Apostille Certificate) # - New MAH's commitment of maintaining same manufacturing and control conditions	[120]: - Certified copy of the MA - Manufacturer's GMP certificate
11	**FI**	None (CL only) [122]	- Transfer declaration between current and proposed MAH (see §) [122, 123]	Transfer declaration (agreement on the transfer declaring MA and associated duties and responsibilities transferred to the proposed holder in their entirety) signed by the current & proposed MAH (§) [122, 123] - After transfer: new MAH should submit name and contact information of QPPV [123]	-
12	**FR**	None (CL only) [67]	Agreement of transfer from current MAH [67]	Proposed MAH's acceptance to comply with all the MA requirements and in particular to the manufacturing and control methods [67]	- Copy of the MA, certified by the current MAH [67] - Additional requirements (such as those concerning manufacturing) [67]

	CA	AF	Current MAH's waiver of responsibility for MP	Proposed MAH's ability to take over responsibility	Other
13	**HU**	National-scope variations AF (available in EN) [127]	Transfer declaration of current MAH (transfers all rights & resp.) [68]	- Confirmation declaration of future MAH (accepts all rights & responsibilities) [68] [126]: - PVS statement declaring if PVS changes or not. If unchanged: declaration from proposed MAH declaration that it has a PVS and QPPV at its disposal (signed by future MAH and QPPV) (original) + authorisation of proposed MAH to the company responsible for PVS (signed by both parties) (original). If changed: variation for new PVS must be submitted (and MA transfer suspended until variation ended positively).	-
14	**IE**	National MA transfer AF (in English) [133]	Transfer declaration of current MAH (in AF) (transfers all rights and responsibilties, full dossier transferred, still responsible for prod. marketed under its name) [133]	Transfer declaration of proposed MAH (in AF) (accepts all rights and responsibilties, full dossier received, confirmation than can comply with pharmacovigilance obligations, has scientific service at its disposal) [133]	Additional requirements if no manufacturer specified in the license [131]
15	**IS**	EU-VAF (without ticking on a variation type) [135]	Signed statement from current MAH incl the date the MA transfer comes into effect (&) [135]	[135]: - Signed statement from future MAH (&) incl.: - date when they take over all resp. for prod. - name of an Icelandic representative of the new MAH (*if applicable*) - wholesale distributor for the Icelandic market (*if applicable*) - Description of PVS of proposed MAH, if it does not have a MP with a MA in Iceland.	-

	CA	AF	Current MAH's waiver of responsibility for MP	Proposed MAH's ability to take over responsibility	Other
16	**IT**	None (CL only) [138]	Dee of transfer of MAH from current to proposed MAH with legalised signatures [138]	-	Statement by QP of all sites involved in all steps of manufacturing that he accepts responsibility to manufacture product on behalf of proposed MAH (specifying the manufacturing steps) (paper copy) [138]
17	**LT**	National MA transfer AF (in Lithuanian) [73]	- Confirmation all docu. transferred to proposed MAH [141, 73]	- PVS summary [141] - Confirmation from proposed MAH that complies with Article 15 of the Lithuanian Law on Pharmacy obligations and contact details of of QPPV and PVS office contact [73] - Risk Management Plan (*if applicable*) [73] - Contact details of scientific service [141]	-
18	**LU**	National forms (in French only) [143]	Copy of the transfer agreement (signed by current & future MAH) [143]		Copy of the approval from the NCA of the country of importation (AT, BE, FR, DE) [143]
19	**LV**	EU-VAF (type II) [144]	- Document confirming MA transfer from the effective date [143] - Document certifying complete transfer of updated docu. prior to transfer or availability of a copy to the future MAH [144]	- Document stating future MAH is prepared to take over responsibilities from the effective date [144] - Document stating new MAH can fullfill all MAH obligations (manufacture and control, import, export and distribution of MPs, advertising of MPs, undesirable side-effects and MPs clinical trials) [144], including: - Contact details of QPPV (in AF) + CV - Contact details of scientific information (in AF)	-

	CA	AF	Current MAH's waiver of responsibility for MP	Proposed MAH's ability to take over responsibility	Other
20	**MT**	National MA transfer AF (in English) [145]	Transfer declaration of current MAH (in AF) - transferring responsibilties from effective date - that full dossier transferred - that remains responsible for product marketed under its name (adverse reactions, quality defects, recalls)	- Transfer declaration of proposed MAH (in AF) - accepts responsibilities for product - that full dossier received - confirmation can meet Pharmacovigilance obligations - confirmation that has scientific service in place	-
21	**NL**	None (CL only) [148]	Declaration from the current MAH agreeing to the transfer [148]	- Declaration from the proposed MAH that they accept to take over all rights and responsibilities [148] - PVS statement (template in [148]) declaring suitable PVS is in place and QPPV available. - Contact details of QPPV [148]	-
22	**NO**	EU-VAF (type IB) [150]	Confirmation from both parties on the agreement of transfer, including confirmation that transfer does not imply other changes to product [150]	-	
23	**PL**	None (CL only) [79]	- Transfer agreement between current and proposed MAH concerning the MA transfer (original or notarised copy (certified translation to Polish, *if applicable*)) [153, 79]	- Proposed MAH declaration taking over all responsibilities (certified translation to Polish) [153, 79] - Declaration complete documentation received [79] - Statement from proposed MAH that no changes made to the MA (apart from MA transfer) (original or notarised copy (certified translation to Polish, *if applicable*)) [153, 79]	Additional requirements (such as proof-of establishment for the current MAH, list of MPs concerned, copies of MAs, POA) [79]

	CA	AF	Current MAH's waiver of responsibility for MP	Proposed MAH's ability to take over responsibility	Other
24	**PT**	None (CL only) [154]	Foll. docs. signed by current and proposed MAH [154]: - Declaration that complete and updated dossier drug transferred to future MAH - Declaration of effective date from which the proposed MAH will assume all responsibilities for the MP concerned	- Certificate or another document to attest proposed MAH can act as a MAH according to the law [80] - Contact details of QPPV (signed by present and proposed MAH) + CV [154] - Contact details of scientific service (signed by present and proposed MAH) + CV [154]	-
25	**RO**	National MA transfer AF (in English) [155]	-	[155]: - A document certifying that the full, updated dossier of the MP has been made available to proposed MAH - A document declaring the effective date when the proposed MAH will take over all responsibility for product - Contact details of QPPV + CV - Contact details of scientific service - Contact details of person in charge of complaints - Contact details of person authorised for communication on behalf of the proposed MAH after transfer approval - Signed statement listing all pending FUMs or SOs, if any	Additional requirements (such as if presentations of the MP not yet marketed) [155]
26	**SE**	National MA transfer AF (in English) [157]	-	-	Confirmation from current MAH to permit packs with the old and new labels to be sold in parallel for a maximum of 6 months (*if applicable*).

	CA	AF	Current MAH's waiver of responsibility for MP	Proposed MAH's ability to take over responsibility	Other
27	**SI**	None (CL only) [160]	Statement from current MAH agreeing to transfer and transferring complete documentation to proposed MAH (signed by the authorised person) [160]	[160]: - Statement from future MAH acceding to transfer of the MA and of receipt of the complete documentation (signed by authorised person) - Contact details of QPPV + CV - Commitment that new MAH to submit variation application for PSMF notification within 60 days after approval of MA transfer (or submission of new PVS with MA transfer application)	Additional requirements (such as a table of products to be transferred, last approved PI with JAZMP (SI NCA) stamp) [160]
28	**SK**	National MA transfer AF (in Slovak and English) [162]	Declaration from current MAH that proposed MAH has access to complete updated dossier (in AF) [162]	[162]: - Declaration that proposed MAH agrees to transfer on the effective date and has access to complete and updated dossier (in AF) - Contact details of QPPV (in EU and in SK) - Transfer agreement (current and proposed MAHs)	Additional requirements (such as valid MA in SK, POA for legal representative for proposed MAH in SK and consent from legal representative to act on its behalf) [162]
29	**UK**	National MA transfer AF (in English) [167]	- Letter from current MAH confirming date of cancellation, the date until when existing stock from current MAH may be sold (maximum six months after the MA transfer) [166]	Confirmation from proposed MAH confirming that a QPPV is available and will update NCA of any PVS changes after end of transfer (submit variations as necessary) and that all supporting data is in their possession,. If changes will occur, confirmation that variations will be submitted after the transfer is approved (in AF) [166]	Additional requirements (such as information concerning the manufacturer, information on risk minimisation activities (*if applicable*), fragments of SmPC) [166]

CA	AF	Current MAH's waiver of resp. for MP	Proposed MAH's ability to take over responsibility	Other
EMA [4]	None (CL only) NB: all information required for EMA is attached to the CL (templates available).	-	- Document certifying that complete and up-to-date file concerning the MP made available to the proposed MAH (signed by current and proposed MAH) - Document stating date when proposed MAH takes over all responsibilities including an overview of activities done by the current MAH during the transitional period (period between date of notification of the Commission Decision on the Transfer and the effective date) (signed by current and proposed MAH) - Contact details of person authorised for communication on behalf of the proposed MAH after MA transfer authorised (signed by proposed MAH) - Contact details of QPPV + CV (signed by proposed MAH) - Contact details of scientific service (signed by proposed MAH) - Contact details of person in charge of quality defects and batch recall signed by proposed MAH) - Confirmation that proposed MAH has services of the new QPPV and necessary means for collection of adverse reactions (signed by proposed MAH and new QPPV) - Statement listing remaining FUMs or SOs, if any (signed by proposed MAH)	Additional requirements (such as NRG confirmation on acceptibility of proposed name (*if applicable*), declaration from current MAH stating if product not yet marketed in EEA).

Abbreviations used in table

AF	application form
CA	Competent Authority
CL	cover letter
CV	Curriculum Vitae
EMA	European Medicines Agency
EU-VAF	EU Variation Application Form
FUMs	follow-up measures
MA	marketing authorisation
MA no.	marketing authorisation number
MAH	marketing authorisation holder
MP	medicinal product
NRG	Name Review Group
PI	Product information (SmPC, PIL and labelling)
PoA	Power-of-attorney
PVS	Pharmacovigilance System
QPPV	Qualified Person for Pharmacovigilance
SOs	Special Obligations

Appendix 4 Sources for table 4 (evaluation of marketing authorisation transfer applications)

	CA	Source for evaluation of marketing authorisation transfer applications
1	**AT**	[56]
2	**BE**	[93]
3	**BG**	[95 (Google translation)]
4	**CY**	[98]
5	**CZ**	[104]
6	**DE - BfArM**	[110]
7	**DE - PEI**	[113]
8	**DK**	[117]
9	**EE**	[63]
10	**EL**	[64]
11	**ES**	[120]
12	**FI**	[123]
13	**FR**	[67]
14	**HU**	[127]
15	**IE**	[131]
16	**IS**	[136]
17	**IT**	[71]
18	**LT**	[73]
19	**LU**	[143]
20	**LV**	[144]
21	**MT**	[145]
22	**NL**	[149]
23	**NO**	[151]
24	**PL**	[79]
25	**PT**	[80]
26	**RO**	[81]
27	**SE**	[159]
28	**SI**	[160]
29	**SK**	[165]
30	**UK**	[166]
31	**EMA**	[4]

Appendix 5 IDRAC references

The following IDRAC references were found in the IDRAC website [18] by searching the "Procedure for Transfer of Marketing Authorization" under "Marketing Authorization Procedures" of the "Regulatory Summaries" for the member states concerned and "European Union" for the centralised procedure (accessed on 29 June 2013).

	Ref.	**EEA member state**	**Document no.**	**Dated**
1	[56]	**AT**	IDRAC 31699	June 2013
2	[57]	**BE**	IDRAC 21947	June 2013
3	[58]	**BG**	IDRAC 56565	March 2013
4	[59]	**CY**	Not available	
5	[60]	**CZ**	IDRAC 42338	April 2013
6	[61]	**DE**	IDRAC 32763	January 2013
7	[62]	**DK**	IDRAC 28414	January 2013
8	[63]	**EE**	IDRAC 117442	May 2013
9	[64]	**EL**	IDRAC 37562	June 2012
10	[65]	**ES**	IDRAC 30627	August 2012
11	[66]	**FI**	IDRAC 25838	June 2013
12	[67]	**FR**	IDRAC 22070	June 2012
13	[68]	**HU**	IDRAC 46091	November 2012
14	[69]	**IE**	IDRAC 13114	May 2013
15	[70]	**IS**	Not available	
16	[71]	**IT**	IDRAC 22174	January 2013
17	[72]	**LI**	Not available	
18	[73]	**LT**	IDRAC 117187	March 2013
19	[74]	**LU**	Not available	
20	[75]	**LV**	IDRAC 117591	October 2012
21	[76]	**MT**	Not available	
22	[77]	**NL**	IDRAC 36672	March 2013
23	[78]	**NO**	IDRAC 51859	November 2012
24	[79]	**PL**	IDRAC 43160	November 2012
25	[80]	**PT**	IDRAC 30128	May 2013
26	[81]	**RO**	IDRAC 58574	October 2012
27	[82]	**SE**	IDRAC 25213	May 2013
28	[83]	**SI**	IDRAC 41120	October 2012
29	[84]	**SK**	IDRAC 46259	June 2013
30	[85]	**UK**	IDRAC 21601	December 2012

	Ref.	**Competent Authority**	**Document no.**	**Dated**
	[86]	**European Medicines Agency**	IDRAC 14897	**June 2013**

Appendix 6 National competent authorities' sources of information for the marketing authorisation transfer (NCA websites' URL and other)

	NCA	[Reference] NCA information source
1	**AT**	[87] MA transfer (in German) (updated 13.08.2012): http://www.basg.gv.at/arzneimittel/zulassung/mrpdcp-verfahren/uebertragungrechtsuebergang/ [88] Forms: http://www.basg.gv.at/arzneimittel/formulare/nationale-zulassung/ (for: national change submission form (22.03.2012) „*F_Z09_Aenderungsformblatt*" and marketing authorisation transfer form (13.04.2012) „*F_Z31_Aenderung_Uebertragung*") [89] 21.06.2013 phone call with Ms. Hartmann, Austrian Medicines and Medical Devices Agency
2	**BE**	[90] Variations ((updated 10.05.2012): http://www.fagg-afmps.be/en/human_use/medicines/medicines/MA_procedures/Variations/ [91] eSubmission Guidelines including documents for MA transfer (updated 24.06.2013): http://www.fagg-afmps.be/en/binaries/eSubmission-guidelines-V-2-2013-06-21_tcm292-226755.pdf [92] Circular letter 542, annex 7, stating documents to be submitted for MA transfers (01.04.2009) (in French) http://www.fagg-afmps.be/en/binaries/circulaire-542-annexe-7_tcm292-62167.pdf [93] 11.04.2013 e-mail from V. Bertrand, Belgian Federal Agency for Medicines and Health Products
3	**BG**	[94] Notification that application form is available: http://en.bda.bg/index.php?option=com_content&view=article&id=99:dear-applicants&catid=5:important-information-category&Itemid=9 [95] "Issue of Variation of Marketing Authorization of pharmaceutical product for transfer of the rights over an issued Marketing Authorization of medicinal product" (in Bulgarian) (08.05.2011) http://en.bda.bg/index.php?option=com_content&view=article&id=25:issue-of-variation-of-marketing-authorization-of-pharmaceutical-product-for-transfer-of-the-rights-over-an-issued-marketing-authorization-of-medicinal-product&catid=4:administrative-services-category&Itemid=6

	NCA	[Reference] NCA information source
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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Berlin, 26.07.2013 _____

Gilda Gordon