Submission of variations to implement changes in the product information texts following European Paediatric Work Sharing Procedures according to Article 45/46 of Regulation (EC) No 1901/2006 – from the point of view of a generic company

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List of Abbreviations

CA	Competent Authority
CMD(h)	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human
CMS	Concerned Member State
CP	Centralised Procedure
DCP	Decentralised Procedure
EC	European Commission
EMA	European Medicines Agency
EPAR	European Public Assessment Report
MAH	Marketing Authorisation Holder
MS	Member State
PIP	Paediatric Investigation Plan
PL	Package Leaflet
RMS	Reference Member State
SmPC	Summary of Product Characteristics

1 Introduction

Whereas for the majority of the medicinal products used in adults sufficient and appropriate information is available, there is a lack of satisfactory information on medicinal products used to treat children within the European Union. At least fifty per cent of the medicinal products used to treat children's diseases, have not been authorised for paediatric indications and clinical trials in children have never been conducted [1]. Therefore, medicinal products for the paediatric population are often used off-label. This common off-label use constitutes an substantial risk for children. Undesired side effects may occur as appropriate pharmaceutical formulations for children are often not obtainable. In addition, the desired efficacy might not be achieved due to inappropriate dosage of the respective medicinal product.

As a consequence of the missing information on medicinal products used in children within the European Union, the decision has been made to promote clinical trials in children in order to ameliorate the development of medicinal product for the paediatric population [2].
Finally, on 26 January 2007, the Regulation (EC) No 1901/2006 (The “Paediatric Regulation”) was enforced after years of discussion regarding medicinal products for children [3].

The purpose of the Paediatric Regulation is to support the development of medicinal products for the paediatric population. The legislation engages pharmaceutical companies to conduct clinical trials in children. Marketing authorisation holders (MAHs) are obligated to conduct studies in accordance with a paediatric investigation plan (PIP), a research and development programme for the performance of clinical trials in children, and should present this data when applying for a new marketing authorisation. In return, MAHs might benefit from an additional six month patent protection period. It should be mentioned that for applications according to Article 10 and Article 10(a) of Directive 2001/83/EC, the applicant is not obliged to present data on clinical trials in children [4].

In addition, the enforcement of the Paediatric Regulation resulted in the creation of a European work sharing procedure for assessment of paediatric data has been established within the European Union. The purpose of this European paediatric assessment procedure is the evaluation of clinical trials conducted in children. Legal basis is given in Article 45/46 of the Paediatric Regulation. Whereas Article 45 describes an assessment procedure for new data on clinical trials in children for designated drug substances, Article 46 sets out the requirements for the submission of paediatric studies finished after 26 January 2007 [3].

The purpose of the European paediatric work sharing procedure according to Article 45/46 of the Paediatric Regulation is to obtain information on conducted paediatric studies. Following the compilation and assessment of this data, the results are then added to the information texts (Summary of Product Characteristics and Package Leaflet) of the medicinal product in order to make the acquired information available for patients [6].

After finalising the work sharing procedure and publication of the respective European Public Assessment Report (EPAR), a variation to the marketing authorisation has to be applied for in order to implement the outcome of the work sharing procedure and amend the information texts (Summary of Product Characteristics and Package Leaflet) accordingly.

This master thesis sets out the legal basis of the European paediatric work sharing procedures according to Article 45/46 of the Paediatric Regulation. It describes the European work sharing assessment process and presents the type of variation to be submitted in order to amend the respective information texts (Summary of Product Characteristics and Package Leaflet). Medicinal products marketed by generic companies are usually not involved in the preceding work sharing procedure, however, the EPAR is also applicable for generic medicinal products.
That means that MAHs of medicinal products containing the same active substance as the originator’s brand also have to amend their marketing authorisations accordingly and submit a suitable text variation.

2 Regulation (EC) No 1901/2006 as legal basis for the European Paediatric Work Sharing Procedure

2.1 General

On 26 January 2007 the Regulation (EC) No 1901/2006 was implemented after publication in the Official Journal of the European Union on 27 December 2006 [4].
Although several legal obligations for the pharmaceutical industry had previously existed, there had been a lack of information on medicinal products used in the paediatric population.

In fact, almost fifty per cent of the medicinal products used in the paediatric population are currently not authorised to treat children's diseases and are consequently used off-label. The use of unauthorised medicinal products in children should not be underestimated. Due to insufficient information on drugs to be used in the paediatric population as well as unavailable pharmaceutical formulations, children are often subjected to medication-dependent undesired side effects based on inappropriate dosage of medicinal products.

Based on the necessity of promoting medicinal products for the paediatric population, a relevant legislation was put into effect with the Regulation (EC) No 1901/2006, also called the “Paediatric Regulation” as aforementioned [2].
In reference to Article 1 of Regulation (EC) No 1901/2006, obligations are laid down for the development of medicinal products in the paediatric population so as to meet the therapeutic necessities of children.

In order to discuss the paediatric population, it is important to define which therapeutic group is meant by this expression. Therefore, a respective definition is given in Article 2 of Regulation (EC) No 1901/2006 where it is stated that “paediatric population means that part of the population aged between birth and 18 years” [3]. In addition, Article 2 of Regulation (EC) No 1901/2006 gives a further important definition of the meaning of a 'medicinal product authorised for a paediatric indication'. A medicinal product is authorised for a paediatric indication when this

indication is mentioned in the Summary of Product Characteristics (SmPC), respectively in the Package Leaflet (PL). Consequently, a medicinal product is off-label used when the respective paediatric indication is not part of the information texts of the medicinal product.

In order to reduce the off-label use in children's medication, general authorisation requirements are set out, such as in Article 7 of the Paediatric Regulation. As stated in this article, MAHs are obliged to include the results of all studies performed in compliance with a PIP in their marketing authorisation dossier. The grant of a waiver and a deferral are also added in addition to the requested documents in accordance with Article 8(3) of Directive 2001/83/EC.
This paragraph does not only affect applications for new marketing authorisations but applies also to applications for marketing authorisations requesting new indications including paediatric indications, new pharmaceutical formulations and new routes of administration [3].

Depending on the subset of the paediatric population as well as the therapeutic indication applied for in the marketing authorisation application, the submission of a PIP may not be necessary in certain cases. Therefore, either a class waiver or a product specific waiver might be requested from the Competent Authority (CA). By granting such a waiver, clinical trials in the respective subgroup of the paediatric population do no have to be conducted. In the case the applicant would like to conduct clinical trials in children after the submission of the PIP, a request for deferral is possible. A good reason would have to be given by the applicant for such a demand [5].

2.2 European Work Sharing Procedures according to Article 45/46 of Regulation (EC) No 1901/2006

2.2.1 Legal basis

By implementing the Paediatric Regulation, a European work sharing procedure for the assessment of paediatric data has been established within the European Union. The purpose of this European paediatric assessment procedure is the evaluation of clinical trials conducted in children. Legal basis is given in Article 45/46 of the Paediatric Regulation.

Article 45 of Regulation (EC) No 1901/2001 requires that all sponsored paediatric trials conducted by the marketing authorisation holder or by a sponsor, respectively, are to be submitted to the CA for assessment. In detail, the wording of Article 45 is as follows:

“1. By 26 January 2008, any paediatric studies already completed, by the date of entry into force, in respect of products authorised in the Community shall be submitted by the marketing authorisation holder for assessment to the competent authority.

The competent authority may update the summary of product characteristics and package leaflet, and may vary the marketing authorisation accordingly. Competent authorities shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisation concerned.

The Agency shall coordinate the exchange of information.

2. All existing paediatric studies, as referred to in paragraph 1, and all paediatric studies initiated prior to the entry into force of this Regulation shall be eligible to be included in a paediatric investigation plan, and shall be taken into consideration by the Paediatric Committee when assessing applications for paediatric investigation plans, waivers and deferrals and by competent authorities when assessing applications submitted pursuant to Article 7, 8 or 30...”

Whereas Article 45 describes an assessment procedure for new data on clinical trials in children for designated drug substances, Article 46 sets out the requirements for the submission of paediatric studies finished after 26 January 2007:

“1. Any other marketing authorisation holder-sponsored studies which involve the use in the paediatric population of a medicinal product covered by a marketing authorisation, whether or not they are conducted in compliance with an agreed paediatric investigation plan, shall be submitted to the competent authority within six months of completion of the studies concerned.

2. Paragraph 1 shall apply independent of whether or not the marketing authorisation holder intends to apply for a marketing authorisation of paediatric indication.

3. The competent authority may update the summary of product characteristics and package leaflet, and may vary the marketing authorisation accordingly.

4. Competent authorities shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisation concerned.

5. The Agency shall coordinate the exchange of information”. [3]

2.2.2 Purpose of Article 45/46 of Regulation (EC) No 1901/2006

The purpose of the European paediatric work sharing procedure according to Article 45/46 of the Paediatric Regulation is to get information on conducted paediatric studies. Following the compilation and assessment of this data, the respective results are implemented in the information texts (SmPC, PL and Labelling) of the medicinal product in order to make the acquired information available for patients [6].

In general, the MAH is obliged to submit all paediatric studies to the Member States (MS) concerned within 6 months after completion of a clinical trial [7,8]. Regardless of the place of conduct of the clinical study, the applicant is supposed to inform the CA about the finalisation. The assessment will then be done on a European level [8].

In order to ease the process of assessment, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD(h)) has established respective guidelines describing the paediatric assessment procedure for the MAH as well as for the respective CA.
Guidelines are applicable for medicinal products nationally authorised via mutual recognition and decentralised procedure (MRP and DCP) as well as for purely national medicinal products. For the latter, national CA may set out different timetables in order to adapt the national information texts. Hence, it is recommended the applicant considers the websites of the respective CA in order to follow national instructions [6].

2.2.3 The European Medicines Agency (EMA) as a promoter of the European Paediatric Work Sharing Procedure

Since MAHs are obliged to present any results of clinical trials in children according to Article 45/46 of the Regulation (EC) No 1901/2006, a suitable assessment procedure has been established and needs to be followed by the MAH as well as by the CA. The work sharing procedure of Article 45 is very similar to the one of Article 46. The latter is only applicable to clinical trials carried out after 26 January 2007. This is the date when the Paediatric Regulation came into effect [7]. Nevertheless, for both procedures, the EMA is taking the lead in organising the work sharing procedure as it is responsible for each European assessment process of medicinal products in the European Union [6].

The procedure of work sharing according to Article 45/46 of the Paediatric Regulation comprises several steps, such as the initial phase of planning and priority setting, the appointment of the Rapporteurs as well as the submission of respective documentation by the MAH. Additionally, in the course of the paediatric assessment procedure, a mandatory timetable should be followed by each participant involved in the process. As a first step, after having prepared an overview of medicinal products intended for a European assessment procedure by the EMA, the joint Paediatric Subgroup CMDh/EMA appoints the Rapporteur for the upcoming assessment work sharing procedure [9]. Several principles are to be considered when choosing the MS acting as Rapporteur, such as respective expertise and knowledge of the active

substance and the amount of work sharing procedures already managed by the MS. The MAH of the medicinal product(s) concerned will be informed about this appointment.

Unless the drug substance is protected by patent law, more than one MAH may be involved in the European work sharing procedure and is informed accordingly. The Rapporteur usually communicates with the originator of the clinical data. In addition to the information of the MS acting as Rapporteur, the EMA informs the MAH about timetable and contact details for submission of clinical data [6].

2.2.4 Submission of documentation by the MAH in advance of initiation of European Paediatric Work Sharing Procedures

In principle, the applicant should submit the documentation in electronic format according to the current Common Technical Document format (CTD) to all MS involved in the procedure. All relevant data necessary for the paediatric assessment procedure, such as study reports, Periodic Safety Update Reports (PSUR), information texts (SmPC, PL and Labelling) as well as an expert overview describing the submitted information, should be presented [6,11].
In case the paediatric studies have been conducted in accordance with a PIP, this information should be mentioned in the cover letter of the submitted documentation. In addition, the MAH is obliged to submit a so-called line-listing. This document presents all marketing authorisations containing the same active substance for which paediatric studies have been conducted. The line-listing has to be updated regularly by the applicant [7].

2.2.5 Ways of communication within the framework of the European Paediatric Work Sharing Procedures

During the period of assessment, the MAH and the MS acting as Rapporteur normally communicate electronically via a certain email address. All correspondence such as timetables, (draft) assessment reports or comments from Member States, should be sent by the MS to this email address. Simultaneously, the MAH is strongly encouraged to submit all applicants' responses to the national contact address of the Rapporteur's CA [11].

In order to ease the progress of assessment, each correspondence should mention a respective procedure number in the heading of an email. The procedure number is usually defined by the Rapporteur and is composed as the following figure describes [6,7]:

Table 1: Procedure number for Article 45/46 work sharing procedure

CC/W/nnnn/pdWS/vvv	
(Example: UK/W/0123/pdWS/001)	
With:	
CC:	A two letter code representing the Rapporteur
W:	A new domain for Work sharing procedures
nnnn:	A counter. Each number equals one active substance
	(e.g: /1234/ = propofol)
pdWS:	Qualifies a paediatric work sharing under Art 45/46
vvv:	Is a sequence number for follow-up issues/assessments

2.2.6 Timetable of Article 45/46 European Paediatric Work Sharing Procedures

Procedures in accordance with Article 45/46 of the Paediatric Regulation follow the timetable of European work sharing procedures based on a Type II variation of 90 days. Afterwards, the MAH should apply for a variation in order to implement the results of the work sharing procedures in the information texts (SmPC and PL). In addition, each MAH of medicinal products containing the respective active substance should follow the originator and submit a suitable variation. When applying for a

variation, the applicant is supposed to confirm that only results of the preceding Article 45/46 procedure have been implemented and no other changes have been made [6].

By way of example the timetable in accordance with Article 46 procedure is presented as follows [7]:

Table 2: Flow chart paediatric assessment procedure

- 14 Calender days	Validate the application and indicate start date procedure. This validation includes a check whether the documentation is complete to start the assessment. Rapporteur creates file in CTS.
Day 0	Rapporteur informs the MAH and MS of start date and timetable. (Circulate timetable via paediatric mailbox.)
By Day 70	Rapporteur circulates preliminary paediatric assessment report (PPdAR) to MS via paediatric mailbox.
By Day 85	Receive contribution from other MS for inclusion in final PdAR or supplementary information request; Rapporteur prepares consolidated list of questions.
By Day 89	Rapporteur sends one request for supplementary information as appropriate (clock stop) together with the draft PdAR to those companies which submitted data with a copy to MS and the MAH. Rapporteur informs MS of request to the MAH. MAH replies to request for information.
By Day 89	Consider response from the MAH. Rapporteur assesses the response to the issues raised. Rapporteur takes the lead in the discussion with MS and considers whether a break out may be needed. Timetable set (as before) for a break out to be possible at Day 105. Rapporteur contacts EMA (CMDh-secretariat) if needed to book a room.
By Day 90 (clock on)	Rapporteur circulates finalised PdAR to MS with draft decision and give the MS a set timeframe to respond for deciding whether a break out has to take place.
Around Day 105	Hold break out meeting (when needed), in case discussion is required between MS to come to harmonised decision.

By Day 115	Receive confirmation from MS of acceptance/non-acceptance of PdAR decision.
By Day 120	Rapporteur finalises the procedure and provides a formal position and the final PdAR to the MAH with a copy to MS. This formal position is then used as supporting documentation in the Type IB variation, if required. Rapporteur requests the MAH to submit a Type IB variation (or extension of application) within 60 days, if appropriate to implement the proposal and amend the marketing authorisation, as necessary.
By Day 180	Rapporteur prepares a public paediatric assessment report, unless otherwise justified, in accordance with standard procedure agreed in CMD(h), if appropriate. The public assessment report will be published on the CMD(h) website.
By Day 270 By Day 270	If considered necessary to guarantee safe use in the paediatric population of the medicinal products with the same active substance, submission of Type IB variation will be requested from other MAH, in order to add text agreed during the paediatric assessment procedure and published on the CMD(h) website (e.g. safety information), to the SmPC/PL of products with the same active substance and pharmaceutical form within 60 days of publication of the public assessment report. In the exceptional situation where no agreement can be achieved between the Member States following discussions in this procedure, the Rapporteur can forward the matter for discussion in the CMD(h) with the aim to achieve consensus.

2.2.7 Compilation of European Public Assessment Reports and Outcome of European Paediatric Work Sharing Procedures

After completing the European paediatric assessment work sharing procedure, a European Public Assessment Report (EPAR) is published. Beforehand, a draft

version is sent to the MAH in order to check whether all confidential data has been deleted. Afterwards, the EPAR is published on the respective CMD(h) website [6,7].
In general, a Paediatric Assessment Report is divided into the following sections [10]:

Table 3: Table of content of European Paediatric Assessment Report

Table of content of the PaedPAR Public assessment report Paediatric data in EU Work sharing procedure	
Coverpage	Information about the product and procedure 1. Name of the product 2. Active substance 3. Pharmaceutical form 4. Strength 5. MA Holder
Coverpage	6. Agencies that acted as Rapporteurs/Co-rapporteurs in procedure 7. Timetable
Scientific discussion	1. Introduction Scope of the assessment II Scientific discussion III Overall conclusion, benefit/Risk assessment IV Proposed changes in the SPC

The purpose of the EPAR is to update the marketing authorisation by amending the information texts (SmPC and PL) in order to provide prescribers and patients throughout the European Community with the necessary information on paediatric use for the medicinal product.
Therefore, the assessment report includes a table, as per below, in order to highlight which sections of the SmPC need to be updated in reference to the outcome of the work sharing procedure. The PIL should be amended accordingly [11].

Table 4: Outcome of assessment of EPAR

Outcome of assessment	**Recommendations for SmPC**
Existing paediatric use	
No new efficacy information. No new safety Information.	No change or a recommendation to revise text in line with current SmPC guidance.
New efficacy information not leading to a change in indication or dose recommendations for children.	Additional study information in section 5.1.
New efficacy information leading to a change in indication or dose recommendations for children.	Revision to indications and dose in sections 4.1 and 4.2 and corresponding study information in 5.1.
Outcome of assessment	**Recommendations for SmPC**
New safety information not affecting benefit: risk.	Additional safety information as appropriate in section 4.3-4.9.
New safety information which affects benefit: risk.	Appropriate changes to indications, dose and safety information in sections 4.1-4.9.
No existing paediatric use	
Efficacy information insufficient. No adverse safety information.	Recommendation not to use in section 4.2 and corresponding study information in section 5.1
Efficacy information shows lack of therapeutic benefit. Adverse safety information.	Recommendation not to use in section 4.2 and study information in section 5.1. Appropriate contraindications or warnings in sections 4.3 and 4.4.
New efficacy information leading to updated indication and dose recommendations for children.	Revision to indications and dose in sections 4.1 and 4.2 and corresponding study information 5.1.

3 Submission of variations according to Article 45/46 of Regulation (EC) No 1901/2006

3.1 General

According to the Directive 2001/83/EC on the Community code relating to medicinal products for human use, each variation to an existing marketing authorisation has to be either notified or approved by the respective CA depending on the type of variation to the marketing authorisation [12]. Since the marketing authorisation also comprises the information texts (SmPC, PL and Labelling) of a medicinal product, each amendment to the information texts also falls under the scope of Article 35 of Directive 2001/83/EC which states the following:

“1. Any application by the marketing authorization holder to vary a marketing authorization which has been granted in accordance with the provisions of this Chapter shall be submitted to all the Member States which have previously authorized the medicinal product concerned.

The Commission shall, in consultation with the Agency, adopt appropriate arrangements for the examination of variations to the terms of a marketing authorization.

These arrangements shall be adopted by the Commission in the form of an implementing regulation. That measure, designed to amend nonessential elements of this Directive by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 121(2a) [12]”...

Depending on the type of change necessary to the marketing authorisation concerned, variations can be classified in different categories, namely Type IA, Type IB or Type II variations. The type of variation depends on the impact of the change with regards to the quality, safety or efficacy of the medicinal product for which a variation is submitted to the CA [13]. For each type of variation a respective timetable is applicable for the assessment procedure.

3.2 Submission of variations according to the legislation of Regulation (EC) No 1084/2003 prior to 01 January 2010

3.2.1 Legal basis

Prior to 01 January 2010, the implementation date of the Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products ("new Variation Regulation"), the Commission Regulation (EC) No 1084/2003 of 3 June 2003 was applicable to medicinal products granted by a CA within the decentralised or mutual recognition procedure [14]. Simultaneously, for marketing authorisations granted by the EMA through the centralised procedure (CP), the Commission Regulation (EC) No 1085/2003 of June 2003 was mandatory for the submission of variation to a marketing authorisation [15].

Following Article 3(1) of Regulation (EC) No 1084/2003, a change to a marketing authorisation means "any amendment to the contents of the documents referred to in Articles 8 to 12 of Directive 2001/83/EC" for medicinal products for human use. In addition, Article 3 defines the different kinds of variations, respectively "minor variation" of type IA and IB and "major variation" of type II. Minor variations of type IA and type IB are listed in Annex I of Regulation (EC) No 1084/2003, whereas type II variations represent all changes to a marketing authorisation not listed in Annex I or where conditions of type IA or type IB variations cannot be fulfilled [14].

Since variations to implement changes in the product information texts (SmPC and PL) following European paediatric work sharing procedures according to Article 45/46 of Regulation (EC) No 1901/2006 are neither listed in Annex I of Regulation (EC) No 1084/2003 nor in the Guideline on dossier requirements for Type IA and IB notifications, respectively, a type II variation after finalisation of the European Assessment Report had to be submitted by the applicant to the respective CA [16].
Therefore, a type II variation to amend the information texts with the recommendations of the assessment report should be submitted after finalisation of the work sharing procedures according to Article 45/46 of the Paediatric Regulation.

Each MAH which had been involved in the assessment procedure had to submit a type II variation within 60 days after publication of the EPAR. In contrast, MAHs of marketing authorisations containing the same active ingredient and pharmaceutical dosage form had to amend their product information texts within 90 days after publication of the assessment report [6,7].

Since for marketing authorisations granted in accordance with Article 10 and Article 10(a) of Directive 2001/83/EC the applicant is not obliged to present data on clinical trials in children [4], marketing authorisations of medicinal products of generic companies are generally not included within a European Paediatric Assessment Procedure according to Article 45/46 of the Paediatric Regulation. Consequently, for generic marketing authorisations, the applicant had 90 days to submit a respective type II variation.

3.2.2 Submission of documentation pursuant to type II variations and respective timetable

Regardless of the type of application for a marketing authorisation, Article 6 of Regulation (EC) No 1084/2003 sets out the approval procedure for major type II variations to a marketing authorisation and defines the documentation to be submitted together with the application [14]:

"1. With regard to major variations of type II, the holder shall submit simultaneously to the competent authorities of the Member States where the medicinal product has been authorised an application accompanied by:

(a) the relevant particulars and supporting documents referred to in Articles 8 to 12 of Directive 2001/83/EC or Articles 12 to 15 of Directive 2001/82/EC;

(b) the supporting data relating to the variation applied for;

(c) all documents amended as a result of the application;

(d) an addendum to or update of existing expert reports/overviews/summaries to take account of the variation applied for;

(e) a list of the Member States concerned by the application for the major variation type II and an indication of the reference Member State for the medicinal product under consideration;

(f) the relevant fees provided for in the applicable national rules in the Member States concerned…"

With respect to the submission of a type II variation, in order to incorporate the changes in the information texts in accordance with Article 45/46 of Regulation (EC) No 1901/2006, the following amendments to the marketing authorisations have to be made for generic medicinal products as well as for their reference medicinal products:

Module 1: Administrative information

1.1	Table of contents
1.2	Application Form
1.3	Summary of product characteristics, labelling and package leaflet
1.3.1	Summary of product characteristics
	Common tracked and highlighted version of SmPC
1.3.2	Labelling and package leaflet
	Common tracked and highlighted version of PL
1.4	Information about the expert
1.4.3	Clinical expert (CV and signature page)

Module 2: Summaries

2.1	Overall table of contents
2.5	Clinical overview
	Addendum to Clinical overview

With the submission of the documentation for the type II variation, common English information texts are provided for assessment. Only after the variation has been

approved, the applicant should submit the national texts to the national CAs within five days.

The current timetable of a type II variation comprises 90 days. As during the European paediatric work sharing procedure, the information texts (SmPC and PL) are discussed, an accelerated type II variation procedure was applicable in accordance with the former legal obligations. Consequently, no additional assessment of SmPC and PIL was necessary provided that no further changes were made.

Table 5: Timeframe of accelerated type II variation procedure

Day 0	RMS notifies the CMS and MAH of the timetable
Day 15	RMS circulates the final SmPC and PL (clean and highlighted changes) to the CMS and the MAH and the procedure is closed.

3.3 Submission of variations according to the legislation of Regulation (EC) No 1234/2008 after 01 January 2010

3.3.1 Legal basis

On 01 January 2010 the Commission Regulation (EC) No 1234/2008 (The “new Variation Regulation”) concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products was implemented and replaced Regulations (EC) No 1084/2003 and (EC) No 1085/2003. For the submission of variations to marketing authorisations granted through either mutual recognition, decentralised or centralised procedure, the new “Variation Regulation” and suitable guidelines on the classification of variations should be followed as of January 2010 [13].

In accordance with the Commission guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, a type IB variation has to be submitted [18].

For variations following an Article 45 procedure, a type IB variation needs to be applied for within 60 days in accordance with section C.I.3 a) of the “Classification Guideline”. The timeframe of 60 days is applicable to all MAHs involved in the preceding assessment procedure. In contrast, MAHs of medicinal products containing the same active substance and pharmaceutical form are asked to submit a suitable type IB variation within 90 days after the publication of the EPAR [6]. Consequently, generic companies generally have to submit their type IB variations for their medicinal products within a timeline of 90 days.

In contrast to variations following an Article 45 procedure, the timeframe of submission differs for variations submitted in accordance with Article 46. As mentioned in the guidelines, the product information texts (SmPC and PL) of all marketing authorisations involved in the preceding Article 46 procedure, have to be updated within 30 days. For all other marketing authorisations, including generic medicinal products with the same active substance, a suitable type IB variation needs to be applied for within 60 days of the publication of the EPAR 8 [7].

3.3.2 Submission of documentation pursuant to type IB variations and respective timetable

Independent of the type of application for a marketing authorisation, Article 9 of Regulation (EC) No 1234/2008 sets out the notification procedure for minor variations of type IB [13]:

“1. The holder shall submit simultaneously to all relevant authorities a notification containing the elements listed in Annex IV.

If the notification fulfils the requirement laid down in the first subparagraph, the competent authority of the reference Member State shall, after consulting the other Member States concerned, acknowledge receipt of a valid notification.

2. If within 30 days following the acknowledgement of receipt of a valid notification, the competent authority of the reference Member State has not sent the holder an unfavourable opinion, the notification shall be deemed accepted by all relevant authorities.

Where the notification is accepted by the competent authority of the reference Member State, the measures provided for in Article 11 shall be taken.

3. Where the competent authority of the reference Member State is of the opinion that the notification cannot be accepted, it shall inform the holder and the other relevant authorities, stating the grounds on which its unfavourable opinion is based…"

With regards to the submission of a type IB variation in order to implement the changes in the information texts following a European paediatric work sharing procedure in accordance with Article 45/46 of Regulation (EC) No 1901/2006, the following amendments to the marketing authorisation have to be made for generic medicinal products as well as for their reference medicinal products:

Module 1: Administrative information

1.1	Table of contents
1.2	Application Form
1.3	Summary of product characteristics, labelling and package leaflet
1.3.1	Summary of product characteristics
	Common tracked and highlighted version of SmPC
1.3.2	Labelling and package leaflet
	Common tracked and highlighted version of PL

Since the submission follows a type IB variation procedure, Module 2 is not concerned. Therefore, neither Module 2.5 Clinical overview nor Module 1.4.1 Information about the expert(s) are part of the application.

In contrast to a type II variation procedure, not only common English information texts are provided for assessment, but national texts of the MS involved in the procedure should be submitted simultaneously as no national phase exists after receipt of notification of the type IB variation.

Section C.I.3 a) of the new “Classification Guideline” is applicable to type IB variations in accordance with Article 45/46 procedures. Therefore, reference to the guideline requirements of this section has to be made by the applicant when submitting a suitable type IB variation. The requirements of section C.I.3 a) are presented as follows:

Table 6: Requirements of section C.I.3 a) of the Classification Guideline

C.I.3 Implementation of change(s) by the EMEA/National Competent Authority following the assessment of an Urgent Safety Restriction, class labelling, a Periodic Safety Update report, Risk Management Plan, Follow Up Measure/Specific Obligation, data submitted under Article 45/46 of Regulation (EC) No 1901/2006, or amendments to reflect a competent authority Core SPC	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Implementation of agreed wording change(s) For which no new additional data are submitted by the MAH		1, 2	IB
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH			II
Documentation			
1. Attached to the cover letter of the variation application: EMEA/NCA request with attached relevant assessment report, if applicable.			
2. Revised product information.			
Note: MAHs are reminded that once new information becomes available which might entail the variation of the MA, this should be submitted forthwith as a variation to the competent authorities, rather than awaiting the assessment of those data through one of the procedures mentioned above.			

The current timetable of a type IB variation comprises 30 days [16]. As during the European paediatric work sharing procedure, the information texts (SmPC and PL) have already been discussed, no additional assessment of SmPC and PL are conducted provided that no further changes have been made.

Table 7: Timeframe of type IB variation procedure

Submission	MAH submits variation to the RMS and CMS and a list of dispatch dates to the RMS only. The RMS creates a CTS record.
Day 0	The RMS starts the procedure, completes the CTS record and circulates an email informing the MAH of the procedure start date.
Until Day 20	CMS notify RMS of their objections, if applicable.
Day 30	If the variation cannot be accepted by the RMS, taking into account the CMS comments, the RMS circulates the "Notification with Grounds" to the CMS and the MAH and the clock stops. If the variation can be accepted by the RMS, taking into account the CMS comments, the RMS circulates an acceptance notification to the MAH and informs the CMS by updating CTS and the procedure ends. Where applicable, the MAH provided the RMS during the procedure highlighted and clean versions of the SmPC, labelling and/or package leaflet in electronic format. The RMS checks the highlighted (changed) text, and circulates these documents with a statement that it has endorsed the changes made, to the MAH and CMS.
Clock stop	Within 30 days of receipt of the "Notification with Grounds" the MAH submits an amended notification to the RMS and CMS and a list of dispatch dates to the RMS only.
New Day 0	The RMS restarts the clock, updates CTS and circulates an email informing the MAH that the procedure has restarted.
New Day 30	If the variation can be accepted by the RMS, taking into account the CMS comments, the RMS circulates an acceptance notification to the MAH and informs the CMS by updating CTS the procedure ends. Where applicable, the MAH provided the RMS highlighted and clean versions of the SmPC, labelling and/or package leaflet in electronic format. The RMS checks the highlighted (changed) text, and circulates these documents together with a statement that it has endorsed the changes made, to the MAH and CMS.

	If the variation cannot be accepted by the RMS, taking into account the CMS comments, the RMS circulates a rejection notification to the CMS and MAH and the procedure ends.
Within 6 months after acceptance	Competent authorities should implement the decision nationally within six months.

4 Strategic procedure of implementation of changes in the product information texts

4.1 General

According to Directive 2001/83/EC on the Community code relating to medicinal products for human use, each change or amendment to an existing marketing authorisation has to be either approved or notified by the CA [12]. In addition, Article 35 of Directive 2001/83/EC is applicable when changing the documentation of the marketing authorisation dossier. Changes to the product information texts also have to be applied for since they form part of the marketing authorisation. This legal basis requires each MAH to submit a suitable variation in order to update their information texts of the concerned medicinal products.

The purpose of Regulation (EC) No 1901/2006 is to gather further information on medicinal products used in the paediatric population. In order to reach this aim, the outcome of an assessment procedure under Article 45/46 of Regulation (EC) No 1901/2006 should be implemented for each medicinal product containing the concerned active ingredient and pharmaceutical form as to make the information available to patients whether or not patients take the originator's medicinal product or a generic pharmaceutical dosage form.

Therefore, there is no option for generic companies not to amend their marketing authorisations and not to submit a suitable type IB variation. The difference between an originator's company and a generic company is the timeframe within which a suitable variation has to be submitted to the CA.

Generally, generic companies are not involved in the European paediatric assessment procedure according to Article 45/46 of the Regulation (EC) No 1901/2006 since they do not perform clinical trials in children.
Due to this reason, the deadline to apply for a suitable type IB variation post publication of the EPAR of an assessment procedure in accordance to Article 45, is 90 days instead of 60 days when involved in the procedure [6]. In contrast, each MAH not involved in a preceding assessment procedure according to Article 46 of the

Paediatric Regulation is engaged to submit a type IB within 60 days instead of 30 days.

Section C.I.3 a) of the new “Classification Guideline” is applicable to type IB variations in accordance with Article 45/46 procedures provided that no further changes are made. Therefore, reference to the guideline requirements of this section has to be made by the applicant when submitting a suitable type IB variation [18].
If the applicant applies for further changes of the information texts, reference to section C.I.3. b) of the “Classification Guideline” has to be made. Consequently, a suitable type II variation should be submitted to the relevant CA.

An important rule to follow regardless of the type of marketing authorisation, is the fact that MAHs are supposed to constantly amend their marketing authorisation dossiers. They should not await the finalisation of a European paediatric assessment procedure but instead submit a variation voluntarily and whenever necessary [6]. The purpose of a European work sharing procedure is to harmonise all medicinal products containing the same active substance in order to disseminate the relevant information throughout the European Union for all medicinal products.

4.2 Purely nationally authorised medicinal products

The outcome of a European paediatric assessment procedure in accordance with Article 45/46 of Regulation (EC) 1901/2006 is also applicable to purely nationally authorised medicinal products. The timeframe of implementing the changes to the product information texts may vary depending on the national CA [6].

Therefore, applicants are encouraged to check the websites of their national CA in order to obtain the necessary information for submitting a suitable variation.

The type of variation that needs to be submitted depends on the MS [19].
The Directive 2009/53/EC sets out the legal basis for the submission of variations for purely nationally authorised medicinal products regardless of the type of marketing

authorisation. Therefore, generic companies as well as originator companies have to follow the requirements of each MS.
In detail, Article 2 (Amendments to Directive 2001/83/EC) and Article 3 (Transposition) of Directive 2009/53/EC define the requirements as per below [20]:

"Article 2
Directive 2001/83/EC is hereby amended as follows:

1. the following Article shall be inserted:

'Article 23 b

1. The Commission shall adopt appropriate arrangements for the examination of variations to the terms of marketing authorisations granted in accordance with this Directive.

2. The Commission shall adopt the arrangements referred to in paragraph 1 in the form of an implementing regulation. That measure, designed to amend non-essential elements of this Directive, by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 121(2a).

3. When adopting the arrangements referred to in paragraph 1, the Commission shall make efforts to make it possible to submit a single application for one or more identical changes made to the terms of a number of marketing authorisations.

4. A Member State may continue to apply national provisions on variations applicable at the time of entry into force of the implementing regulation to marketing authorisations granted before 1 January 1998 to medicinal products authorised only in that Member State. Where a medicinal product subject to national provisions in accordance with this Article is subsequently granted a

marketing authorisation in another Member State, the implementing regulation shall apply to that medicinal product from that date.

5. Where a Member State decides to continue to apply national provisions pursuant to paragraph 4, it shall notify the Commission thereof. If a notification has not been made by 20 January 2011, the implementing regulation shall apply.'

2. the second and third subparagraphs of Article 35(1) shall be deleted.

Article 3

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 20 January 2011 at the latest. They shall forthwith communicate to the Commission the text thereof. When Member States adopt those measures, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive [20]".

In order to have a better overview of which MS has already implemented the Regulation (EC) No 1234/2008, the CMDh published a table mentioning all MS to which the new "Variation Regulation" is applicable. For purely nationally medicinal products in Austria, Bulgaria, Czech Republic, Germany, France, Latvia, Malta, Poland, Portugal and Romania, the Commission Regulation (EC) No 1084/2003 as well as Commission Regulation (EC) No 1085/2003 are still applicable regardless of the applicant (Generic company or Originator) [21].

5 Conclusion

Since the outcome of a European paediatric work sharing procedure in accordance with Article 45/46 of the Regulation (EC) No 1901/2006 is applicable to each marketing authorisation containing the concerned active ingredient and the same pharmaceutical form, suitable variations should be submitted by each MAH concerned.

For marketing authorisations granted through a mutual recognition or decentralised procedure, the new Variation Regulation (EC) No 1234/2008 should be followed and a suitable type IB variation submitted in order to amend the product information text of the medicinal products concerned. This procedure is applicable to every medicinal product regardless of the type of application to a marketing authorisation, e.g. generic companies have to submit variations for each of their concerned products.

For purely nationally authorised medicinal products, it is dependent on the implementation of the legal obligation in the MS concerned whether a type IB or a type II variation should be submitted following a work sharing procedure according to Article 45/46 of Regulation (EC) No 1901/2006. According to the Regulation (EC) 1234/2008 a type IB variation has to be applied for provided that no further changes are made, whereas according to the Regulation (EC) No 1084/2003 and Regulation (EC) No 1085/2003 a type II variation should be submitted to the CA concerned.

Regardless of the type of application of a marketing authorisation, variations needs to be submitted but the timeframe within which a suitable variation has to be submitted by the applicant depends on whether or not the MAH has been involved in the preceding European work sharing assessment procedure.

For medicinal products not involved in the assessment procedure according to Article 45, suitable variations are to be submitted within 90 days of finalising and publishing of the EPAR are to be submitted. In contrast, the timeframe of submission of a variation following an Article 46 procedure is shorter: in this case, MAHs have 60 days to apply for a suitable type IB variation.

6 Summary

For the majority of medicinal products used in adults sufficient information is available. In contrast, for medicinal products used to treat children within the European Union, there is a lack of satisfactory information. At least fifty per cent of the medicinal products used for the paediatric population are used off-label. As a consequence of the lack of information, the decision has been made to promote clinical trials in children. As a result of years of discussion, on 26 January 2007 the Paediatric Regulation was finally enforced. The purpose of this legislation is to support the development of medicinal products for the paediatric population by engaging pharmaceutical companies to conduct clinical trials in children. In addition, the enforcement of the Paediatric Regulation resulted in the creation of a European work sharing procedure for assessment of paediatric data. Legal basis for this assessment process is given in Article 45/46 of the Regulation (EC) No 1901/2006. Whereas Article 45 describes an assessment procedure for new data on clinical trials in children, Article 46 sets out the requirements for the submission of paediatric studies conducted post 26 January 2007. Following the assessment procedure the results are added to the information texts (SmPC and PL) in order to make the outcome of the Article 45/46 assessment procedure available for patients. After finalising the European paediatric work sharing procedure, the EPAR is published on the EMA website. MAHs involved in the preceding procedure as well as MAHs of medicinal products containing the same active substance and pharmaceutical form, have to submit a suitable type IB variation in order to amend their marketing authorisations. The variation applied for has to be in accordance with section C.I.3 a) of the Classification Guideline. The submission of a respective type IB variation is mandatory regardless of the type of application of the marketing authorisation, i.e. marketing authorisations of generic medicinal products also have to be amended in accordance with the assessment procedure. Due to the fact that the submission of suitable variations is essential for all medicinal products containing the same active substance in order to provide the necessary information to the patients, there is no choice of submitting the variation or not. The difference between a generic company and a company involved in either an Article 45 or 46 procedure is the timeframe within which the information texts have to be updated accordingly.

7 References

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[13] Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

[14] Commission Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State

[15] Commission Regulation (EC) No 1085/2003 of June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93

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[21] Implementation of the Variation Regulation 1234/2008 in each Member State for medicinal products authorised by purely national procedures, Doc.Ref. CMDh/164/2010/Rev1 February 2010

8 Tables

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

Ulm, den 10.12.2010 _____