National dossier requirements in the European countries –

Last step in obtaining the marketing authorisation or rather a burden for the applicant?

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„*Only who knows his goal will find his way”*
Laotse

For Stefan, Elena, Maria and Gabriel for their support and understanding

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1. List of Abbreviations

AF	Application Form
AIFA	Agenzia Italiana del Farmaco- Italian Medicines Agency
ANSM	French Agency for the Safety of Health Products-France
AR	Assessment Report
ASMF	Active Substance Master File
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BVL	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit
CEP	Certificate of Suitability
CESP	Common European Submission Platform
CHMP	Committee for Medicinal Product for Human Use
CL	Cover Letter
CMDh	Coordination group of Mutual recognition and Decentralised procedures – human
CMDv	Coordination group of Mutual recognition and Decentralised procedures – veterinary
CMS	Concerned Member State
DAR	Draft Assessment Report
DGSanco	Directorate General for Health and Food Safety
DDPS	Detailed Description of the Pharmacovigilance System
EA	Environmental Assessment
eCTD	Electronic Common Technical Dossier
EDQM	European Directorate of the Quality of Medicines
EMA	European Medicines Agency
EU	European Union
HMA	Heads of Medicines Agencies
ICBMV	Institute for Control of Biological Products and Veterinary Medicines-Romania
INFARMED	National Authority of Medicines and Health Products - Portugal
LoA	Letter of Authorization
MAA	Initial marketing Authorization Application
MAH	Marketing Authorization Holder
NeeS	Non-eCTD electronic Submission
QP	Qualified Person
QRD	Quality Review of Document

PEI	Paul Ehrlich Institute
PIL	Product Information Leaflet
PMF	Plasma Master File
PoA	Power of Attorney
PoE	Proof of Establishment
PoP	Proof of Payment
PrAR	Preliminary Assessment Report
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
REN	Renewal
RMS	Reference Member State
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
URPL	The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products - Poland
VAR	Variation
WEU	Well Established Use

2. Introduction

The European regulatory system aims to ensure providing safe, efficient and good quality medicines to its citizens [1]. Providing patients with the necessary medicinal products involves registering them in the different member states of the European Union. The National Competent Authorities are dealing with the authorisation of medicinal products through national, decentralised and mutual recognition procedures, with conduct of post-marketing activities, clinical trials, providing national scientific advice and conducting inspections for companies in their area of responsibility [1].

Even if the NCAs are trying to avoid duplication of assessment and focus on sharing workload and scientific expertise [1], there are still many national requirements that the applicants are to fulfil in order to obtain the national registration of the product in all concerned Member States. The aim of a harmonised single market, that is one of the principles of EU foundation, is still not yet realised, due to the additional local requirements for registering a product in the EU Member States, different timelines for granting the approval, legal status of medicines, other assessment disagreements [2].

In case the Concerned Member States are not agreeing with the assessment of the Reference Member States due to potential serious risks to public health, the scientific coordination work is done based on an Article 29(1) procedure by the coordination group for mutual recognition and decentralised procedures, human (CMDh) or veterinary (CMDv), respectively [1, 2]. As in this master thesis only the requirements for the medicinal products for human use will be considered, the reference will be made in the following to the CMDh.

The scope of the pharmaceutical companies is to timely bring their medicinal products on the market, by obtaining the marketing authorizations. Therefore, the preparation of the dossier (clinical, non-clinical and chemical manufacturing and control modules) for submission must be planned well in advance. The requirements for modules 2 to 5 are so far harmonised across EU Member States. The differences appear usually in module 1, in the specific Additional Data that are requested and in the provision modality of these documents (only copies, originally signed, notarized).

Submission of the application is not limited to the dossier. Samples and mock-ups of the medicinal product, payment of fees and the different modalities of dossier submission, electronic or paper submission, both and/or in parallel, should be clarified and taken into consideration in order to assure a smooth dossier submission.

Compliance of the dossier with the current guidance, the available requirements on the National Competent Authorities webpages and other format related information is often a burden for the applicant not only due to different places where this information might be found, but also due to the continuous change and update of it.

The focus of this work will be on the clarification of the national requirements of the dossier submission through the mutual recognition and decentralised procedures, as being the ones where the different national requirements can be best emphasized. Practical experience with different NCAs during the above mentioned procedures for submission of a new chemical entity or a generic medicinal product, the additional requirements and the timelines for obtaining the approval is detailed in the following sections. Screenings of national competent authorities' websites and comparing the information available at the regulatory database of Thomson Reuters (Cortellis Regulatory Intelligence) have been used as additional sources for completing the national specific requirements for submission of applications.

After obtaining the first registration other regulatory activities are due for submission as the life-cycle of the medicinal product will start. Changes due to continuous improvement of the manufacturing process, registration of additional strengths or pharmaceutical forms, changes in the product information, first renewal of the registration as mentioning only few examples are to be submitted to the respective National Competent Authorities where the product is registered. The additional requirements regarding renewal and variations will be also listed and accordingly commented based on the gathered information and in light of a harmonized single market.

3. Mutual Recognition Procedure versus Decentralised Procedure

European Union was founded between 1952 (the European Coal and Steel Community) and 1956 (European Economic Community) and includes currently 28 countries [3]. The European Economic Area, established 1 January 1998, comprises besides the countries of the European Union also Iceland, Lichtenstein and Norway [4]. All these EEA Member States are implementing the regulatory requirements valid in the European Union.

The basis for registration of the medicinal products in the European countries was first laid down by the Directive 65/65/EEC [5] according to which medicinal products can be nationally registered in one Member State. Starting with the Regulation 75/319/EEC [6] the registration of medicinal products in several EU countries is possible. The Mutual Recognition procedure was first mentioned within the Directive 93/39/EEC [7].

Since 1995 there were 3 different routes to obtain authorization for marketing a product in the Member States of European Union: the Centralised, Mutual Recognition and purely national procedures [8].

The **Centralised Procedure** (CP), having the legal basis in the Regulation (EEC) No 2309/93 [9] and subsequently Regulation EC No 726/2004 [10] is mandatory for biologicals, orphans, medicinal products containing a new substance not registered in the Community before 20 May 2004 and other products as listed in the Article 3 and the Annexes of this Regulation [10]. The registration of a medicinal product through the CP results in a single marketing authorization that is valid in all EU MS [2, 10, 11].

The **Mutual Recognition Procedure** (MRP) is obligatory since 1 January 1998, for medicinal products already having a marketing authorization in one MS and with the intention to be marketed in the other Member States [12]. The MRP was implemented in the EU MS with the Directive 2001/83/EC [13].

Besides CP, MRP and purely national authorisation procedures, the **Decentralised Procedure** (DCP) is another route for marketing a medicinal product in the EU that was introduced later by Directive 2004/27/EC [14]. The DCP applies in case at the time of application no marketing authorisation exists in any of the Member States. In the DCP, the National Competent Authorities are recognizing the first assessment performed by one MS that will act as Reference Member State [2, 14, 15].

The Mutual Recognition and Decentralised Procedures are widely used procedures [2] that are applying in case of the following situations [16]:

- new active substances (if not mandatory for the centralised procedure)
- known active substances as indicated in Article 8(3) of Directive 2001/83/EC
- biological medicinal products (incl. biosimilar) (if not mandatory for the centralised procedure)
- generic medicinal products
- well established use (WEU) (“bibliographic applications”)
- known active substances in new combination

- informed consent to national MA
- (line) extension applications to national
- homeopathics
- traditional herbal medicinal products. [16]

Before starting one of the above mentioned procedures for marketing registration the applicants should define first the Member State that will assess the application dossier, namely the Reference Member State (RMS) and second, the other Concerned Member States (CMS) where the product is intended to be registered. The RMS has an essential role in the MR and DC procedures, being the MS which is evaluating the application dossier and is preparing the Assessment Report (AR) or the preliminary Assessment Report (PrAR), respectively [17].These documents are the key documents "explaining why a marketing authorisation and each of the proposed indications have been or can be approved or rejected by the RMS and detailing the benefit-risk assessment for the product" [18].

Before starting the Mutual Recognition Procedure (MRP) the application is granted in the RMS based on the national draft-AR or preliminary-AR, that was accordingly updated at each assessment stage with "*new information from the applicant, oral explanations and discussion in Committees*" and results then in the assessment report that will be sent together with the application dossier to each of the CMSs [18].The Concerned Member States will indicate their positions and send comments to the RMS and the applicant. The CMSs should agree with the assessment of the RMS and disagree only in case of "*potential serious risk to public health*" [19]. The procedure takes 90 days if there is no dispute between the member states [19, 20]. After the procedure has been concluded the CMSs have 30 days to review translations of texts and to issue a marketing authorization for the respective state [19, 20].

In the case of the Decentralised Procedure (DC) the application is sent concurrently to the Reference Member State (RMS) responsible for the assessment report and the other CMSs [18]. The RMS will prepare a Preliminary Assessment Report (PrAR) at day 70 of the procedure. A draft Assessment Report will be consequently prepared at day 120 and will contain updates from the scientific discussions, recommendations and List of Outstanding Issues [21]. The Decentralised Procedure takes 210 days in absence of disputes. Similar with the MRP, after procedure conclusion, the CMSs have 30 days to review translations of texts and consequently issue the national marketing authorization [19, 21].

In case health concerns have been raised by CMSs so that the AR, SmPC, labeling or patient leaflet is not possible to be approved by Day 90/120, the disagreement is referred to a specific committee, the CMDh (Coordination Group for Mutual Recognition and

Decentralised Procedure human), that includes representatives from the medicinal products agencies from all the Member States [19, 20, 21]. If the dispute is not resolved by CMDh, the issues are referred to the EMA's Committee for Human Medicinal Products (CHMP) [20, 21].

A short presentation of the most important steps in the approval process of Mutual Recognition and Decentralised Procedures are chronologically presented in a comparison table in ***Annex I -*** *Mutual Recognition Procedure versus Decentralised Procedure*. [20; 21].

MR and DC Procedures are widely used modalities for registering generics, new chemical entities, well established use, medicinal products via hybrid applications, fixed combination medicinal products. This is confirmed also by the statistic reported in 2014 by the CMDh [22], according to which, between January 2014 and December 2014, 249 Mutual Recognitions and 797 Decentralised Procedures have been finalized (***Figure 1***). 47% (MRP) and 72 % (DCP) of the finalised procedures are for generics followed by full dossier (28 %) in MRP and hybrid (16%) applications in DCP [22].

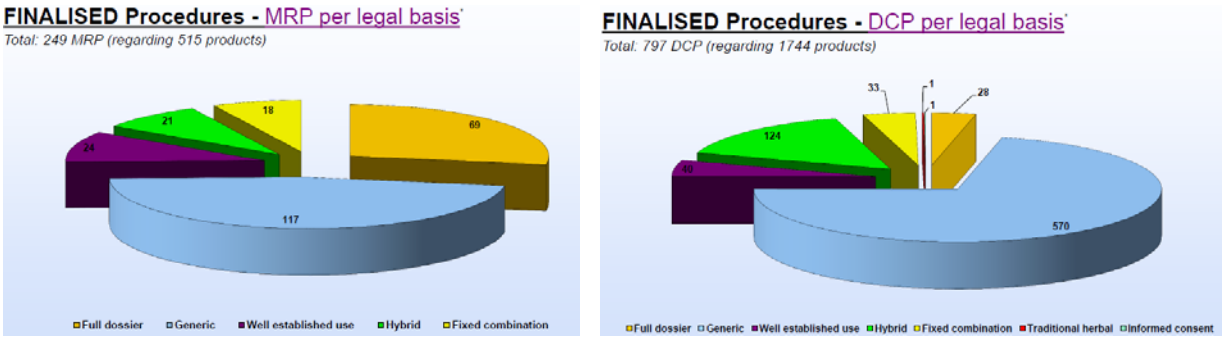

Figure 1. Finalized procedures (including initial MAAs) in 2014 with MRP and DCP as legal basis (according to [22]).

Important to be noticed is that the number of MR/DC procedures started in 2014 is comparatively similar with the number of finalized procedures, showing the same trend of using these procedures: the majority of applications are for generics followed by full dossier in MRP or hybrid dossiers in DCP (***Figure 2***).

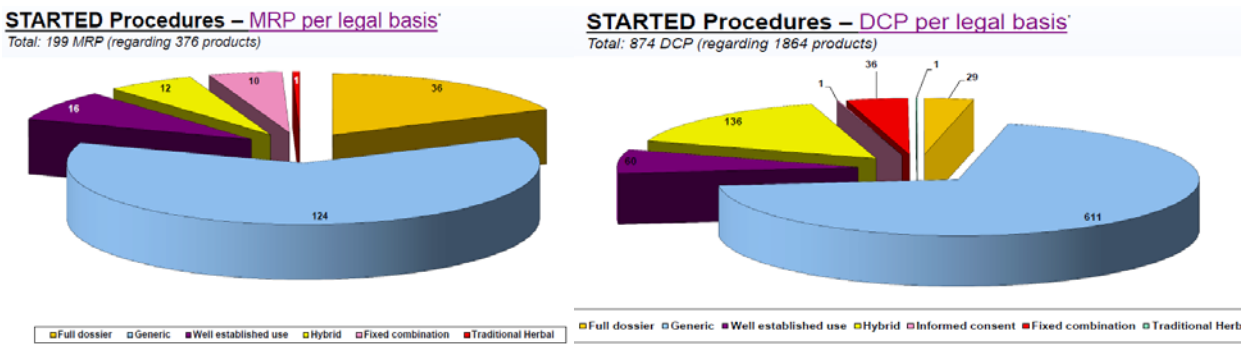

Figure 2. Started procedures (including initial MAAs) in 2014 with MRP and DCP as legal basis (according to [22]).

In the following sections of the master thesis more details about specific aspects of submitting initial applications, variations and renewal within these two procedures with emphasis of the national requirements will be presented.

4. National Competent Authorities of the European Union and their national requirements

Starting of MR/DC procedures means submission to the respective National Competent Authorities that are evaluating the application according to their role as reference or concerned Member States by preparing the Assessment Report or providing comments to it. The Contact Data of the National Competent Authorities are listed on the EMA [23] and the HMA [24] websites and presented in "***Annex II -*** *List of National Competent Authorities of the European Union including Iceland, Lichtenstein and Norway*" with references to the NCAs English websites. For Lichtenstein and Luxembourg only homepages in national language have been found.

Even if the general requirements for dossier preparations are the same within Europe, there are still national particularities required by the NCAs of the Member States [25].The general content of the dossier is indicated in the Notice to Applicants Volume 2B [25, 26]. The Additional Data of Module 1 is the place in the dossier where the applicants should provide the requested specific national documents. CMDh has published on their website in August 2014 [27] the additional data requested by the NCAs to be provided during the initial MAA and in March 2014 the ones for Variations and Renewal Applications [28]. Even if these CMDh overviews are a great support for the applicant, these are not extensively presenting the entire information for a complete submission to the NCAs. There are other specific aspects that are to be taken into consideration and are not listed in those overviews. Therefore screening the website of the NCAs is a must for each applicant and this should be done in regular interval, as the requirements are continuously changing. Here are to be mentioned the specific Application Forms/Cover Letters/Statements that have a given format and are to be completed in national languages (e.g. France, Luxembourg, Spain) or filling in of national database (Spain). Therefore pro-active solutions (e.g agent in the country, experienced translator, etc) are recommended to be found in advance for such issues.

For determining how the day-to-day work of the regulatory affairs professionals is influenced by the large spectrum of the additional national requirements a list of questions was prepared and based on these a short survey was conducted. Other sources of information have been consulted and the results are presented.

5. The survey and other sources of information

The survey was conducted within the experienced professionals belonging to the company where the author of this master thesis is employed with expertise in submitting different regulatory procedures during MR/DC procedures. The asked questions have been chosen in such a manner that the results can be easily compared with the existing CMDh listing of additional data. In addition general questions about the MR/DC procedure, timelines to obtain the approval after the positive opinion of the procedure and granting the national MAAs, payment of fees, experience with electronic submission via CESP and using of national portals. The questions are listed in "***Annex III*** - *Questions of the survey"*.

The interviewees have been chosen in such a way that their experience is covering different types of applications and regulatory activities by working for pharmaceutical companies, with a broad spectrum of medicinal products from generic to new chemical entities including duplicates, parallel applications and/or line extensions. These companies are globally acting and in consequence possessing subsidiaries/agents in many of the EU countries. This means that some administrative regulatory activities are carried out by the respective local representatives. From the interviewed persons all have current experience with the decentralized procedure, a number of 4 with both procedures. Most of the interviewees are involved in life-cycle management activities, but there have been also 2 colleagues with experience in line extension activities for already approved strengths, 2 initial MAAs, one for a new chemical entity and the other for a generic medicinal product and a repeat use for a decentralized procedure. The number of member states included in the above mentioned procedures is varying from 27 countries in the DCP of initial MAA for a generic product and all EU countries including Iceland, Lichtenstein and Norway in one of the line extensions, to 8 participating countries in the repeat use procedure or 23 countries included in a type II variation. With this broad spectrum of experience all relevant regulatory activities are

presented and there is practical experience with the national competent authorities of all member states.

The survey shows that the additional data requested in the CMDh papers [27, 28] is not comprehensive enough to satisfy all national specific requirements. The continuous screening of the official homepages of the respective NCAs involved in the procedure should be continuously done by the applicant. Even so this still does not cover all details of the submission as the information is not completely translated in English and available only in the local language. For example, specific formularies and statements that are to be filled in before submission do not have English versions. Therefore, the navigation through those websites is not each time very conclusive. Solutions for the applicant with daily regulatory work might be to have access to a comprehensive regulatory database or to have local affiliates/partners in the countries where the product is to be brought on the market. Not only for knowing the current requirements and have contact with the national competent authorities, but also to recognize trends in development of local requirements.

Besides the survey and the screening the NCAs homepages, the regulatory database of Thomson Reuters, the Cortellis Regulatory Intelligence [29] has been consulted. This database is providing "*regulatory information for multi-country filing, comparing existing and emerging competitive products, preparing for committee meetings and inspections and keeping up-to-date on regulatory changes as they happen."* [30]. Additional information has been collected either from the specific documents for each EU country that are available for different topics or for comparative tables that are available for fees.

In the following sections of this master thesis more detailed information about gathered information will be presented and critically discussed relative to the national specific requirements of the EU MS.

6. National requirements for initial applications

The specific national requirements for submission of initial applications are presented in the second column of the Table in "***Annex IV-*** *National requirements for submission of the initial Marketing Authorization Application"*. The listing contains data according to the CMDh/043/2007 [27] and CMDh/085/2008 [31], the requirements obtained by screening the NCAs websites, CEPS Contact website, the Cortellis Database and from the survey. It can

be easily recognized that even if the CMDh specific requirements are not comprehensive enough, a regulatory database paired with checking of websites and daily experience is sufficient to complete the specific national requirements.

The additional data requested by the NCAs according to CMDh overviews [27, 31] are mostly related to different provision of administrative information/documents; please refer to ***Table 1*** for a short overview. For exact information please see "***Annex IV-*** *National requirements for submission of the initial Marketing Authorization Application"*. Taking into consideration that some documents can be easily obtained, the certification and even legalization of translated documents must be planned in advance. Issuing cover letters in local languages means a good coordination with local representatives and obtaining copies of contracts between MAH and the different manufacturing sites represents time consuming discussions within the responsible departments. A good planning and follow-up is the key of success for a timely submission.

Table 1 Overview of required additional documents for initial application according to CMDh overviews [27, 31]. For exact information please see ***Annex IV***.

Additional documentation required for initial application	**Countries**
Signature for different types of LoAs	BG, CZ, HR, HU, LT, PL, RO, SK
Contract (original, certified, or only copies) between the MAH and different manufacturing sites	BG, HR, LT
Pharmacovigilance responsible in National Territory	BG, CY,EL, HR
Statement for the MA transfer to the local subsidiary	EL, FI, SK
Person/site responsible for placing the product on the market	FR
Proof of establishment	HR
Extract from the register of entrepreneurs	PL, SK
Proof that the applicant is the same as the MAH	PL
Cover letter in local language	HR, SK
Cover letter, originally signed	HU
Application form, originally signed	BG, HU, LT, PL, RO
Application form signed by the MAH in the RMS	IT
Completion of National Data Base	ES
Statement from MAH naming its local representative in Croatia	HR
Declaration of patent and data exclusivity	HU
Originally signed confirmation of identical dossier	BG, HU, LV, LT, RO
Documents/Statements to be provided in original or as legalized copies	IT (when acting as RMS); LT
Trade mark	EL
Certified copy of the marketing authorization granted by RMS	LT
Samples (finished product and API) to be submitted before day 0	HU
Declaration of conformity of national translations of the SmPC, Pl and labelling	BE

By screening the **NCAs websites, the CESP Contact website and Cortellis Regulatory database** additional specific requirements have been found (for more details please refer to ***Annex IV***). These requirements are presented in ***Table 2***.

Table 2 Overview of required additional documents for initial application according to NCAs websites, CESP contact website and Cortellis Regulatory database. For details please refer to ***Annex IV***.

Additional documentation required for initial application	**Countries**
Filling of specific information in the Application/Declaration Forms	CY, DE, DK, EE, FI, FR, IE, IT, LT, LU, LV, PT, RO
Application Form in local language	ES
Specific Cover Letters	DE, FI, IT, LV, PL
Cover letter in local language	SI, SK
Payment forms	BE, CZ, EE, FR, IE, LT, LV, NO, RO, SK
Declaration of patent and data exclusivity	BG
Requirements for labeling documents or mock-ups	IE, MT, SE, UK
Paper submission of some additional documents	PL

The survey shows additional requirements based on **practical experience**, beside the ones from CMDh overviews and the screening of websites and regulatory database. These are summarized in ***Table 3***. For more details please consult ***Annex IV***.

Table 3 Overview of required additional documents for initial application based on practical experience. For details please refer to ***Annex IV***.

Additional documentation required for initial application	**Countries**
Commitment to submit mock-ups in the national step	BE, ES
Signed Cover Letter from the authorized representative	CZ
Cover Letter in Spanish	ES
Proof of establishment	FR, NL, PT, SI, SK
Letter of Authorisation	FR, SI
Braille declaration	HU
Statement of identity with the dossier in RMS	IT
Translation in Polish of the RMP (occasionally, not valid for each application)	PL

The above mentioned information is showing that some of the additional requirements are similar, differing mostly in the way the respective documents are presented, signed or certified. Documents in local languages are still requested by NCAs.

Aiming to have harmonized requirements it is recommended that the NCAs are discussing and agree upon reducing additional demands by abandoning the request of providing AF, CL or other declaration in national languages, requiring a standard LoA covering all necessary communication aspects and accepting copy of documents without further certification.

After submitting the application, the dossier is validated by the RMS and CMSs within 14 days [20, 21] before starting the MR/DC procedures. A list of invalidation issues at the submission of the applications has been identified by the “Ad Hoc Working Group on Validation issues/National requirements in MR/DC procedures” and published in September 2010 [32]. Between the important invalidation issues is to be mentioned: missing or incorrect fees, application form/cover letter not accordingly signed, missing or not justified absence of some documents (e.g. Braille, Consultation with Target Patient Groups, Pharmacovigilance System, Environmental Risk Assessment, etc) and missing some Annexes to Application Form, Manufacturing/import licenses, GMP certificates missing or proposed batch releaser and MAH outside EEA, ASMF and/or letter of access to ASMF missing or incorrect version submitted, Confirmation of identical dossiers in RMS and CMS, PIL and SmPC not in QRD format, number of submitted copies is insufficient, electronically submitted applications are not according to the national requirements, missing additional data [32].

The above mentioned issues are showing again that compilation of all the national specific requirements is of upmost importance in submission of a valid application and timely starting of the procedures.

After presentation of the additional data required for the life-cycle regulatory activities - variations and renewals, more details about selected topics related to the invalidation issues mentioned above will be presented. The selected topics related to the valid manufacturing authorizations/GMP certificates of the APIs and finished product manufacturers, drug substance documentation (ASMF, CESP or complete 3.2.S Part), product information, mock-ups, sample and specimens, fees and submission possibilities are extensively discuss with focus on the specific national requirements of the Member States.

7. National requirements for maintaining marketing authorizations

7.1. Variations

Still during the reviewing of the application for obtaining the initial marketing authorisation, changes in the submitted documentation might be required due to experience with full scale production, alignments to the need of the market and other changes related to adjustment to the state of the art of technology, science and knowledge [33]. Such variations that imply changes of the labelling documentation, manufacturing process of the drug substance and drug product, specifications, test procedures, stability, batch sizes are to be submitted as variations to the respective national competent authorities that have granted the initial marketing authorisations [33].

Commission Regulation (EC) 1234/2008 [34] amended by the Commission Regulation 712/2012 [35] are governing the procedure for variations of marketing authorisations [36]. In August 2013 the European Commission updated the variation guideline [36] and the requirements in terms of conditions and documents to be provided for the different types of variations: minor variations (Type IA, IB), major variations (Type II), extensions and urgent safety restrictions. Even though this variation regulation is applying for all MS of the European Union, there are still NCAs that are requesting specific national documents. These have been published by the CMDh in March 2014 [28] and are presented in the second column of ***Annex V*** – "*National requirements for Variations and Renewals"*.

- It can be stated that except the proof of payment, the majority of the MS **do not have additional data** in comparison with the EU requirements: Austria, Belgium, Denmark, Estonia, Finland, Germany, Hungary, Ireland, Iceland, Luxemburg, Latvia, Malta, Netherlands, Norway, Sweden, United Kingdom.

- Nevertheless some MS are requesting for variations **more than two additional administrative documents**: Croatia, France, Greece, Lithuania, Poland and Romania.

An overview of these requirements according to the CMDh guidelines: CMDh/197/2010/Rev.3 [28] and CMDh/006/2008/Rev 14 [37] are presented in ***Table 4***. For more details please see refer to ***Annex V*** – "*National requirements for Variations and Renewals"*.

Table 4 Overview of required additional documents for variations according to CMDh overviews [28, 37]. For details please refer to ***Annex V***.

Additional documentation required for variations	**Countries**
Specific LoA	LT, PL
Original or copy of PoA	CZ, LT, RO
Copy of contract between MAH or the applicant and the manufacturer responsible for batch release (in case the last is changed)	HR
Contact person for Bulgaria on behalf of MAH	BG
Trademark of the product for VAR regarding change of the product name	EL, LT
Proof of establishment with details about company and the members of management	PL
Application form, originally signed	BG, HR, LT, PL
Application form in national language	EL, ES
Cover letter, original or certified copy	HR
Cover letter in national language	HR, SI
Original or legalized copies of all Annexes of AF and Statements when acting as RMS	IT, PL
Information to support applications for approval of "umbrella" brands (in case of VAR type IB no A.2b)	RO
National data base should be completed	ES
Originally signed CL and PoP	LT
Electronic copy of proposed PI in word format	CZ, DK, DE, EL, FI, FR, HR, IE, IS, LV, LT, MT, NO, PL, PT, SE, SI

Consulting the **other sources of information** (CESP Contacts, NCAs websites and Cortellis database) it was found that in addition to PoPs, other documents as presented in ***Table 5*** are requested. More details are presented in "***Annex V*** - *National requirements for Variations and Renewals".*

Table 5 Overview of required additional documents for variations according to NCAs websites, CESP contact website and Cortellis Regulatory database. For details please refer to ***Annex V***.

Additional documentation required for variations	**Countries**
Application form, originally signed	CY,PT
Specific Application form in national language	SK
Cover letter, originally signed	CY,PT
Specific Forms	FR, RO
Filled in Payment Form	LV, RO

Additional specific documentation was also found **during the survey**. These **experience-based** additional documents for variations are listed in ***Table 6***. More details are given in ***Annex V***.

Table 6 Overview of required additional documents for variations based on practical experience. More details are given in ***Annex V***.

Additional documentation required for variations	**Countries**
Copy of marketing authorization (or of renewal)	EL
Table summarizing the scope of type IA/IB variations	EL
Explanation form with payment details	LT
Signed PSMF summary in case of VAR updating the PSMF	PL
Proof of Payment	BG

As mentioned at the national requirements for initial applications some of these requirements are time consuming (legalized copies of documents or statements) or difficult to obtain (proof of establishment of the MAH with details about the company and the members of management, copy of contract between MAH and the manufacturer responsible for batch release), therefore the harmonization and even reduction of some requirements is desirable.

7.2. Renewals

The marketing authorisation is valid for a period of 5 years, after which this must be renewed based on the risk-benefit evaluation of the concerned medical product [38]. In case of a positive balance evaluation, the marketing authorisation will have an unlimited validity, unless it is decided based on pharmacovigilance issues related to exposure of an insufficient number of patients, to re-evaluate the risk-benefit balance and renew the product again after another 5 years [38]. The application for renewal should be done at least 9 months before expiring of the marketing authorisation [38]. In case the MAH will not apply in time for the renewal, the MA will elapse [38].

During the national phase of the MRP/DCP the NCAs are granting the marketing authorisation at different point in times, but the renewal must be submitted before expiring of the first granted marketing authorisation. Therefore, establishing of a common renewal date between the marketing authorisation holder, the RMS and the involved CMSs is of utmost importance [38]. For MRP, the common renewal date should be agreed taking into consideration the "*common renewal date of all presentations of the product, the International Birth Date and/or the European Birth Date*" [38]. This "*is set by the RMS at the completion of the initial mutual recognition procedure based on the date that the national MA was originally granted*" [38]. It can happen that the MAH may apply for REN earlier than 5 years, so that

submission will take into consideration the earliest renewal date in any one of the MS, unless another alternative date has been agreed between MAH and RMS [38]. For DCP the common renewal date is proposed by RMS based on completion of procedure. For both procedures, MAH may comment on the proposed common renewal date within 30 days of Day 90 (MRP) or 30 days of end of procedure (DCP) [38].

The documentation that is generally required for the submission of the renewal is presented in Annex 2 of the "CMDh Best Practice Guide on the Processing of Renewals in the Mutual Recognition and Decentralised Procedures, CMDh/004/2005/Rev.11, January 2015" [38], the most important being for the evaluation of the risk/benefit balance of the product the Amendment to the Clinical Overview, the Risk Management Plan and the PSUR [38, 39].

Beside the general renewal documentation, some Member States are requesting specific additional documents. These are presented in the CMDh/197/2010/Rev.3 [28] and CMDh/006/2008/Rev 14 [37] and listed in the 2nd column of ***Annex V***- *"National requirements for Variations and Renewals"*.

- It can be stated from the above mentioned CMDh overviews [28, 37] that except the proof of payment and the electronic copy of the proposed Product Information (as indicated in [37]) **16 of the 30 Member States** (Lichtenstein is not additionally listed as following the requirements in Austria) **do not have additional requirements** for the submission of renewal.
    - These countries are: Austria, Belgium, Denmark, Estonia, Finland, Germany, Hungary, Ireland, Island, Luxembourg, Latvia, Malta, Netherlands, Norway, Sweden and United Kingdom.

The requested additional documents for renewals based on the CMDh overviews [28, 37] are listed in ***Table 7***. For more specific details please consider the information presented in ***Annex V***- *"National requirements for Variations and Renewals"*.

Table 7 Overview of required additional documents for renewals according to CMDh overviews [28, 37]. For details please refer to ***Annex V***.

Additional documentation required for variations	**Countries**
Specific LoA	HR, LT, PL
Original version or copy of PoA	CZ, LT, RO
Copy of contract between MAH or the applicant and the manufacturer responsible for batch release	HR
Written statement from MAH naming its local representative and proof that MAH has responsible person for Pharmacovigilance in HR	HR
Originally signed QP declarations	BG, PL, RO
Proof of establishment with details about company and the members of management	PL
Authorized agent with place of residence in Poland	PL
Contact person for Bulgaria on behalf of MAH	BG
Application form, originally signed	BG, HR, LT, PL
Application form in national language	EL, ES
Cover letter, original or certified copy	HR
Cover letter in national language	HR, SI
Original or legalized copies of all Annexes of AF and Statements	IT, PL
PSUR cover letter, signed by the EU-QPPV to be submitted in original	IT
National data base should be completed	ES
Originally signed CL and PoP	LT
Electronic copy of proposed PI in word format	CZ, DK, DE, EL, FI, FR, HR, IE, IS, LV, LT, MT, NO, PL, PT, SE, SI

Screening the CESP Contacts, NCAs websites and Cortellis database it was found that in addition to PoPs, other additional requirements need to be prepared. These are presented in ***Table 8***. Detailed information can be found in ***Annex V***.

Table 8 Overview of required additional documents for variations according to NCAs websites, CESP contact website and Cortellis Regulatory database. For details please refer to ***Annex V***.

Additional documentation required for variations	**Countries**
Application form, originally signed	CY, PT
Specific Application Form in national language	SK
Cover letter, originally signed	CY, PT
General information form with copy of MA	CY
Specific Forms and Declarations	HR, FR
Filled in Payment Form	ES, LV, RO

- **Experience based** information for renewal was **not found** within the survey.

With 11 (9 without PoP and electronic copy of PI) additional requirements, Croatia is the most challenging country, besides Poland and Lithuania each country with 6 additional requirements.

Similar with the preparation of variation documentation, the additional requested documents might be difficult to obtain due to their confidentiality character (copies of contracts, proof of establishment with details related to company and members of management) or their time consuming nature (certification and legalization of statements and declarations). Harmonization of all these requirements is desirable.

In the following sections other important aspects selected based on the invalidation issues published by CMDh [32] will be discussed, considering specific national aspects related to submission of applications.

8. Valid manufacturing and import licenses for the manufacturing sites/ Inspections

The legal basis for authorizing medicinal product for marketing through mutual recognition and decentralised procedures is given in Title IV of Directive 2001/83/EC [13], amended by the Directive 2004/27/EC [14] and Directive 2011/62/EU [40]. This implies that all manufacturing sites of the respective medicinal product have valid manufacturing authorisations, confirming that the product is manufactured according to the GMP guidelines. In addition, the product release is certified by a Qualified Person [41].

Inspections of the manufacturing sites in the EU are carried out by the supervisory authority of the competent authority of the Member States. During submission of the marketing authorisation GMP inspections may be conducted if the site was not yet inspected [41]. Within the Pharmaceutical Inspection Co-Operation Scheme (PIC/S) the participating authorities are recognizing the GMP certification of the other authorities. In the EU there is a Memorandum of Understanding between PIC/S and Heads of Medicines Agencies (HMA) for recognizing the audits of inspectorates between the EU Joint Audit Programme and the PIC/S assessment programme [42].

After granting the MA these inspections are taking place regularly in order to verify compliance with the conditions mentioned in the marketing/manufacturing authorisations and the good manufacturing practice. The interval between the inspections is in general 3 years except the cases where based on risk-analysis these are requested to be done earlier [41].

Products that received a marketing authorisation through the MR/DC procedures can be marketed in the respective CMSs and RMS. The surveillance that the product is manufactured GMP conform according to the approved specifications is done by testing samples from the product marketed by wholesalers, community pharmacies, hospital pharmacies etc. A work-sharing program was established by EDQM in order to reduce duplication and cost of analytical evaluation of testing products in the MR/DC procedures and sharing the test results between the Member States and other concerned bodies (e.g. HMA, EMA) [43].

9. Active ingredients manufacturers (ASMF or CEP)

The manufacture of active ingredients should be done in accordance with GMP guidelines and accordingly monitored. The legal basis was first mentioned in 2005 under the provisions of Directive 2004/27/EC [14] and strengthened under Directive 2011/62/EU [40] (both Directives amending Directive 2001/83/EC [13]) and Regulation (EU) No 1252/2014 [44]) [41].

Manufacturers of active substance must be registered in the Member States in which they are established [41]. Active substances manufactured in third countries must get the confirmation that the API manufacturing is according to the EU standards [45]. The Supervisory Competent Authority in the Member State of the MAH of the finished product is responsible for this verification by inspecting the respective manufacturers in the third country. In order to optimize the resources of conducting inspection and the exchange of information an international API inspection program including authorities from EU, USA and Australia has been created [41].

Besides the valid manufacturing authorisation, drug substance manufacturers are required to provide the Drug Master File or the valid Certificate of Suitability (CEP), if they are not preparing the complete Drug Substance information as part 3.2.S of the dossier.

For active substances, starting materials or excipients that are organic and inorganic substances, fermentation produced substances that are indirect gene products, products with risk of transmitting agents of animal spongiform encephalopathies, herbal drugs, herbal drugs preparations and are subject to a European Pharmacopoeia monograph, applicants can apply for a certificate of suitability (CEP) [46, 47]. Based on the provided information on substance manufacturing and the impurity profile, the European Directorate for Quality of the Medicine (EDQM) is issuing the CEP that certifies the chemical and microbiological purity of the respective substance with reference to the European Pharmacopoeial monograph. The CEP is then presented in the respective Drug Substance Part of module 3 of the dossier [46, 47].

In case such a certification does not exist or the substances are not subject to the European Pharmacopoeial monograph, the European Drug Master File in CTD format and the respective Access Letter to the closed part are to be submitted as part of the dossier to the National Competent Authority of the Member States [47] or as alternative the complete Drug Substance Part.

During performing of the survey **specific national requirements** for submission of CEP have been identified for some MS based on their RMS role.

- **Italy** and **Finland** are requesting to submit all CEP versions between the currently approved and the proposed one in a grouped variation.
- **Italy** and **Poland** are requesting the filling in of the access box, which appears at the bottom of the certificates to help CEP holders to trace the use of their certificates by the customers, with additional information.
- In addition, **Italy** is requesting that the CEP holder is entering information about MA holder, product name, MA number and the name and the position of the responsible person who signs, should be clearly stated. In case the CEP holder is located outside EEA, its signature should be notarized, otherwise an original signature will be enough.

Similar information about the different requirements/acceptance of CEP from some NCAs was found in a presentation hold to an **EDQM International Conference** [48]: beside the a.m. requests for Italy, practical experience with using CEP was provided:

- France required Type II VAR when the limit of palladium mentioned on CEP was increased from 1 to 2 ppm and
- Spain is refusing a CEP where the Thin Layer Chromatography method was mentioned for the related substances [48].

10. Product Information

Another issue that constantly appears between the invalidation issues in the submission of initial applications [32], but also for variations [49] and renewals [50] are related to the labelling of the product. In the following sections, the labelling of the product: Summary of Product Characteristic (SmPC), product information leaflet (PIL), mock-ups and specimens are discussed in details taking into consideration the specific national requirements.

The legal requirements for labelling of a medicinal product are introduced by the Directive 2001/83/EC [8]. The SmPC and PIL must be in accordance with the current QRD Templates for the MRP/DCP [51], should follow the Readability Guidelines [52], the Excipients Guideline [53] and any other national requirements as it is for example in Germany the special submission of PIL and SmPC in a defined format, the so called “Zulassungsmaske” and their providing as doc or docx files as additional working documents in module 1.3.1 [54].

The proposed texts for SmPC, PL and labelling can be submitted in English by the initial submission of the dossier during MR/DC procedures, but high-quality translations of the agreed text are to be submitted 5 days after end of procedure [55]. The Q&A document specifies also the possibility that some NCAs might ask to have these translations before finalization of procedure.

The additional labeling information required by the Member States is listed in the Annex I of the “Guideline on the Packaging Information of Medicinal Products for Human Use Authorized by the Union” [56]. There are presented all requested information that should be entered in the “blue box”, from price of the medical product and reimbursement conditions to legal status and pictograms. Besides this guideline, CMDh updated in 2014 the “blue-box” requirements, the national additional information for the labelling/packaging materials requested by the EU Member States for submission of a new application [57].

- It is easily recognizable from these requirements that between the **most challenging national competent authorities** are the ones from **France, Italy, Slovenia and Spain** [57].
- There are also counties that **do not have additional requirements** neither for labelling nor for package leaflet: **Cyprus, Estonia, Lichtenstein, Luxembourg and Malta** [57].
- The five Nordic countries: **Denmark, Finland, Iceland, Norway and Sweden** agreed to have a common Nordic package due to the small market of each of these countries [58]. A common pack can be created with labelling in all 5 languages for primary and secondary packages and patient leaflet [58]. The national "blue box" requirements on the patient leaflet must be taken into consideration for all Nordic countries. It is recommended to prepare before submission mock-ups for primary and secondary packaging in all 5 languages in order to test their viability [58].
- Similar with the Nordic package, the three Baltic States, **Estonia, Latvia and Lithuania** have agreed on a common Baltic package procedure [59].The procedure is coordinated by the Estonian Agency of Medicines.

Even if preparation of common packs represents an additional regulatory work for the applicant, not only at the time of first submission but also with each change that affects the package, such common packages are widely used by pharmaceutical companies due to commercial reasons.

11. Mock-ups, specimen, samples

11.1. New Applications

Besides the package leaflet, mock-ups of the sale presentations are requested to be submitted within the application in Section1.3.2 Mock-ups of the dossier [26]. The "mock-up" represents the copy of the full colour artwork including Braille, "*presented so that, following cutting and folding where necessary, it provides a replica of both the outer and immediate*

packaging" [60]. The Member States may request also specimens, which is the "*sample of the actual printed outer and inner packaging materials and package leaflet*" [60].

CMDh published first in 2012 and then reviewed in July 2013 [60] the information related to the requested mock-ups, specimens and samples that should be provided within the MRP/DCP for initial marketing authorisations. This information is presented in the 3rd column of ***Annex IV*** - *"National requirements for submission of the initial Marketing Authorization Application"*. Some EU countries (LU, LI) are not listed in this table, as Luxembourg relays on the expertise from Germany and/or Belgium and Lichtenstein is accepting the MA granted by Austria.

A contradiction appears for Sweden (SE) between the requirements listed here [60] and the information found on the NCA website [61] that a sample (or even a placebo) of medicinal product, one package per medicinal product/strength/pharmaceutical form, should be submitted with the application. The intention of the SE national authority is to check the patient friendly design of the package and not the final labeling [61].

11.2. Variations and Renewals

For specific type of VARs that are affecting the "overall design and readability of the outer and immediate packaging or package leaflet" mock-ups or specimens are requested to be submitted to the Member States [36]. Samples are required for certain variation when changes might affect the specifications of the finished product. The information related to the type of variations which might require samples by submission is provided in the Guideline "Mock-ups, specimens and samples" [62] and listed in the 3rd column of ***Annex V*** - ***"****National requirements for Variations and Renewals"*.

- Countries like **Denmark, Finland, Germany** (BfArM), **Portugal and Sweden** are not mentioned, not being clear if the information is not available or these countries are not asking samples for the mentioned variations.

The guideline [62] appears under the CMDh website under Renewal and Variation, but the title mention only the requirements for variations not making any reference that these are not applicable for renewals.

12. Fees

12.1. New Applications

Another important aspect in preparation of the submission is the payment of correct fees due to the fact that this is another aspect in the invalidation of submission. The fees to be paid to each National Competent Authorities of the EU counties for the initial applications of a new active substance or a generic product are presented in ***Annex VI*** – *"Fees for Initial MAAs"*. These fees are for the first pharmaceutical form and strength if no otherwise mentioned. The fees expressed in the national currency are the valid one; their transformation in Euro is only user-orientated as the changes have been calculated with the transfer rate of 30 May 2015.

The table in the ***Annex VI*** is showing that:

- The fees are to be paid in advance and the proof of payment is to be submitted with the dossier as Attachment to the Application Form.
- Only very few countries are sending invoices to the applicant (Austria, Germany, Denmark, Iceland, Netherlands, Norway, Sweden and Slovenia).
- Netherlands presents a special case because according to the Medical Law of Netherlands a proof of payment is to be submitted with the application, this practice is at the moment not in force and an invoice is provided after dossier submission [63].

Beside the proof of payment there are NCAs requesting:

- filling of additional Fee Forms (France, Ireland, Latvia, Romania and Spain) and/or
- electronic payment through national portals (Cyprus, Italy, Latvia, Portugal, Slovakia and Spain).

Generally it can be stated that the fees are less expensive for applications in MRP comparing with DCP, for generic in comparison with full applications and when the MS is acting as CMS compared with MS acting as RMS. For a rough estimation please see also ***Table 13*** – *"Fees for initial applications".*

The fees are continuously changing and adapted to the new NCAs requirements. For example, Germany has currently changed the fees through the new regulation (3rd regulation for changing the AMG-fee regulation-Dritte Verordnung zur Änderung der AMG-Kostenverordnung) issued March 3rd 2015 [64]. Therefore it is recommended checking of the respective fees each time before submission of applications. Paying of incorrect fees

or/and not paying them within the mentioned timelines will delay the start of procedure (invalidation issue) or will cause additional costs for the applicant.

12.2. Variations and Renewals

The fees for submission of renewals and variations are presented in ***Annex VII*** – "*Fees for Renewals"* and ***Annex VIII*** – *"Fees for MRP Variations"* respectively. The requirements regarding proof of payment have not been additionally mentioned as they are similar with the ones presented in ***Annex VI*** – *"Fees for Initial MAAs",* 2nd column.

It is important to mention that for the **renewal**:

- some Member States are not requesting additional fees for evaluating the renewal (Austria, Netherlands and Sweden) or
- are not requesting fees for renewal when acting as CMS (Finland, Ireland and United Kingdom).

For more details please refer to the ***Table 14*** - "*Fees for Renewal*".

From the overview of **variations in MRP** can be concluded:

- that variation fees are included in the annual fee in Austria, Netherlands (except extensions), SE (for type IA and IB) or
- no fees are requested in Luxembourg (all VAR types), Malta (when acting as CMS for type IA, IB and II VARs), Norway (VARs type IA, IB - if changes in PI are excluded) and United Kingdom (type IA VAR).

Similar with the fees for initial applications, paying the correct amount of fees is important in order to get starting of valid procedures and avoiding their re-payment.

After collecting of all additional specific documents and payment of correct fees and getting the proof of payment (if applicable), the next aspect that is to be consider is the submission of the dossier to the RMS and the involved CMSs.

13. Different modalities for dossier submission (CESP, national portals or paper/CD submission)

13.1. Common European Submission Portal (CESP)

The submission of the dossier through the Common European Submission Portal has been increasingly used in transmitting information between the applicant and the member states of the EU. Through this portal of the HMA website, electronic submissions can be provided simultaneously to the Reference Member State and the other Concerned Member States involved in the procedure [65].

At the moment (June 2015) 27 Member States, EDQM and DGSanco can receive documentation through this portal, but this number is continuously increasing [66]. The last regulatory authority that joined CESP was ICBMV, Romania on 2nd of February 2015 [66].

- Some Member States are participating to this submission platform with 2 (Czech Republic, France, Romania and United Kingdom) or even 3 competent authorities in case of Germany (PEI, BfArM and BVL).
- Unfortunately, there are still Member States for which submission through CESP is not yet possible (Bulgaria, Greece, Slovakia) or possible only for veterinary products (Hungary).

Even if submission through CESP has been accepted as submission channel from most of the EU National Competent Authorities,

- there are regulatory authorities using CESP still in a pilot phase (ANSM-France, AIFA-Italy, URPL-Poland, INFARMED-Portugal) or
- using the portal only as supportive submission as it is in case of Italy.
- Submission of the Application Forms, Cover Letters and/or other documents in original are still required in Croatia, Cyprus, Czech Republic, Latvia, Lithuania, Portugal and Slovenia.

An overview of these submission particularities is presented in ***Annex IX*** – *"Submission modalities"*.

13.2. Submission through the National Portals

Electronically submission through the national portals is requested or recommended by the national authorities in Germany, Italy, Portugal, Spain and United Kingdom.

- In **Germany** using the PharmNet.Bund portal [67] for dossiers submission is recommended and awarded by the authority with reduction of fees for variations [68].
- MHRA (**UK**) also recommends using their portal [69] for submission of applications.
- In **Spain** updating of the national database is a specific requirement for both initial MAAs and variations mentioned in the CMDh lists [27, 28]. In consequence submissions through AESMP-Portal [70] are mandatory.
- The pre-submission on the initial MAAs through the **Portughese** SMUH-AIM portal [71] needs to be done before dossier submission.
- **Italy** strongly recommends submission of the variation applications through the national portal [72] .However, the submission in paper and on CD should be done in parallel with CESP submission [72]. According to the new updated CMDh reference document “Requirements on submissions (number and format) for New Applications within MRP, DCP and National Procedures” [31] the initial applications are mandatory to be submitted via the national portal. This information is neither found on AIFA new information systems [73] (on this website only variations and renewals are mentioned) nor under CESP Contact Information, where only submission of variation is mentioned.

Even if **Slovakia** is not taking part to CESP, it is required to submit Variations through the national portal [74].

13.3. CD/DVD and paper submission

Even if submission in electronic format (eCTD, NeeS) is strongly recommended applications in paper format and/or via CD/DVD are still accepted. This information was currently updated (end of April 2015) for submissions of new applications, variations and renewals [31, 37]. Nevertheless, applicants are strongly encouraged to use the electronic submission and to switch to it when submitting variations and renewals applications.

According to the EMA eSubmission Roadmap [75] submission of the new applications within DCP will be mandatory from 2015, Q3 and within MRP from 2017, Q1. Using of the eApplication Forms will be mandatory for all procedures starting from 1st July 2016 [76].

An overview about the submission modalities taking also into consideration the available information on CESP Contacts [66] is presented in ***Annex IX*** – *"Submission modalities"*.

In these new published overviews about "Requirements on Submissions" [31, 37] on the CMDh websites a mistake was made in the information that in Greece submission via CESP is possible for new applications, variations and renewals. This information is not confirmed by the CESP Contact website [66].

Therefore, as the information about submission modalities is steadily changing and updated, this is to be critically reviewed and re-checked before each new submission.

14. National phase - Final step of procedure; Time to national approval

After the end of procedure, Day 150 in MRP and Day 210 in DCP, granting of the national approvals should be done by National Competent Authorities of the respective Member States within 30 days [23, 24]. For this last step in the approval process national high quality translations of the agreed text are to be submitted 5 days after end of procedure [55]. Based on the practical experience, granting of the national approvals is sometimes time consuming. The information gathered within the survey for timelines for getting national marketing authorizations within a Decentralized Procedure and granting national approvals of type II variations is presented in ***Annex X*** – *"Timelines for granting national marketing authorizations and national approvals for Type II variations"*. It is easily recognizable that:

- there are few NCAs, which are granting the national approvals within **1 month**:
  - LT, NL, UK for the new application and
  - BE, HR and PT in case of type II VAR.
- Most of the MS are issuing the national certificates **after 2-3 months**.

For more details regarding the evaluation of survey results, please refer to ***Tables 15, 16*** and ***Figure 7***.

15. Discussions

As presented before, preparation for submitting an application should take into consideration all multiple aspects necessary for completion of the dossier and its timely submission. It has been already mentioned that the complete information is stored in different places and the sources are to be cross checked and compared with the practical experience.

Further in this master thesis the gathered information will be evaluated and for a better understanding graphically presented.

15.1. Additional specific requirements

The additional specific national requirements listed in details in ***Annex IV*** – *"National requirements for submission of the initial Marketing Authorisation Application"* have been evaluated and are presented in ***Table 9*** and ***Figure 3***.

Lichtenstein will not be considered in the evaluation as a separate country, as the approval granted by AGES-Austria is recognized in this country [77]. The proof of payment was not considered as an additional requirement, but as not automatically requested by all countries, important to be taken into consideration at the preparation of the dossier. It can be easily seen that the majority of NCAs have between 3 and 5 specific requirements and that 7 Member States have up to 6 additional requirements. All requirements have been considered as having the same importance/weight, even if in the daily work obtaining a specific legalized document or one with confidential information may request more efforts as a written confirmation or statement.

Table 9 Specific additional requirements for new applications (all requirements have been considered having similar importance/weight)

Specific requirements for initial applications	**Countries**	**Number of countries**
NCAs with no other requirements	AT, IS	2
NCAs with no more than 2 additional specific requirements	BE, CY, DK, EE, LU, NL, NO, SE, UK	9
NCAs with 3 to 5 additional requirements	CZ, DE, EL, ES, FI, IE, IT, LV, MT, PT, RO, SI	12
NCAs with more than 5 additional requirements	BG, FR, HR, HU, LT, PL, SK	7
	Total	30

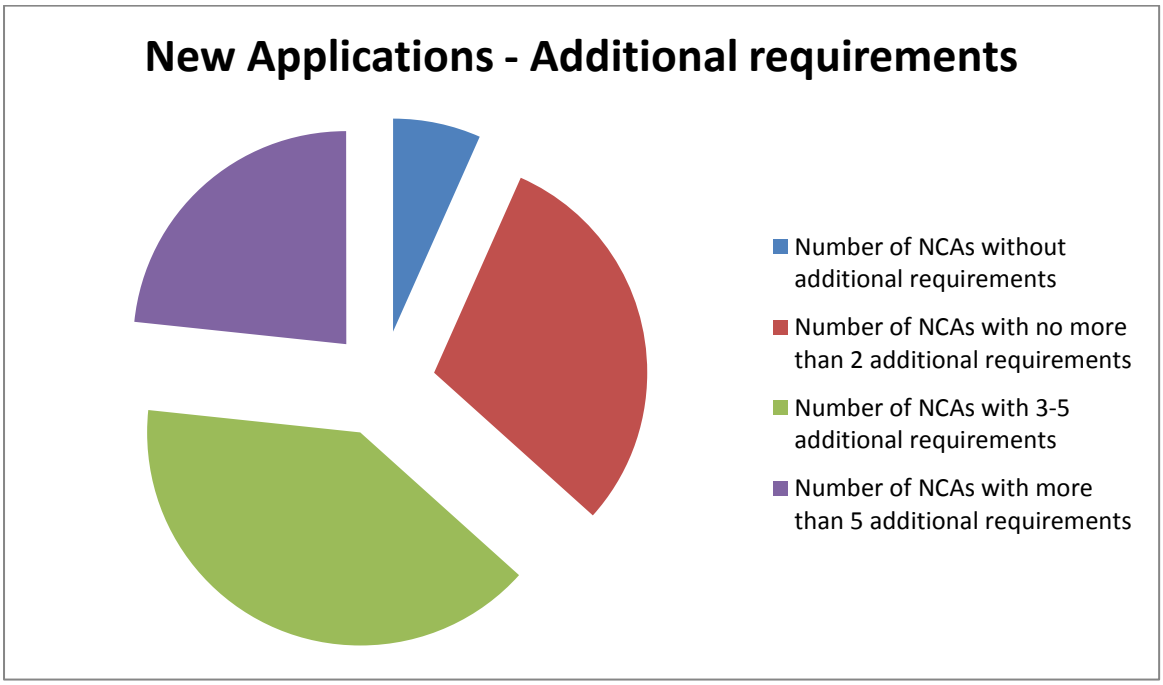

Figure 3 Distribution of the number of the National Competent Authorities (NCAs) based on the number of additional requirements for New Applications.

A similar evaluation was performed also for the specific national requirements for Variations and Renewals that are listed in ***Annex V*** - *"National requirements for Variations and Renewals"*. The evaluation was performed without proof of payment and the electronic Product Information requested according to [37] and the results are presented in ***Tables 9 and 10*** and ***Figure 4***. Even if the number of NCAs in all 3 categories remains the same, nevertheless the countries in category 2 (no more than 2 add. reqs.) and 3 (more than 2 add. reqs.) are different. Only the member states following the EU requirements are the same for variations and renewals.

Table 9 Additional requirements for Variations (PoP and electronic PI not considered as additional requirements)

Additional requirements for VARs	**Countries**	**Number of NCAs**
NCAs following EU requirements	AU, BE, DE, DK, EE, FI, HU,IE, IS, LU, LV, MT, NL, NO, SE, UK	16
NCAs with no more than 2 additional requirements	BG, CY, CZ, ES, FR, IT, PT, SI, SK	9
NCAs with more than 2 additional requirements	EL, HR, LT, PL, RO	5
	Total	30

Table 10 Additional requirements for RENEWAL (PoP and electronic PI not considered as additional requirements)

Additional requirements for REN	**Countries**	**Number of NCAs**
NCAs following EU requirements	AU, BE, DE, DK, EE, FI, HU,IE, IS, LU, LV, MT, NL, NO, SE, UK	16
NCAs with no more than 2 additional requirements	CY, CZ, EL, ES, FR, PT, RO, SL, SK	9
NCAs with more than 2 additional requirements	BG, HR, IT, LT, PL	5
	Total	30

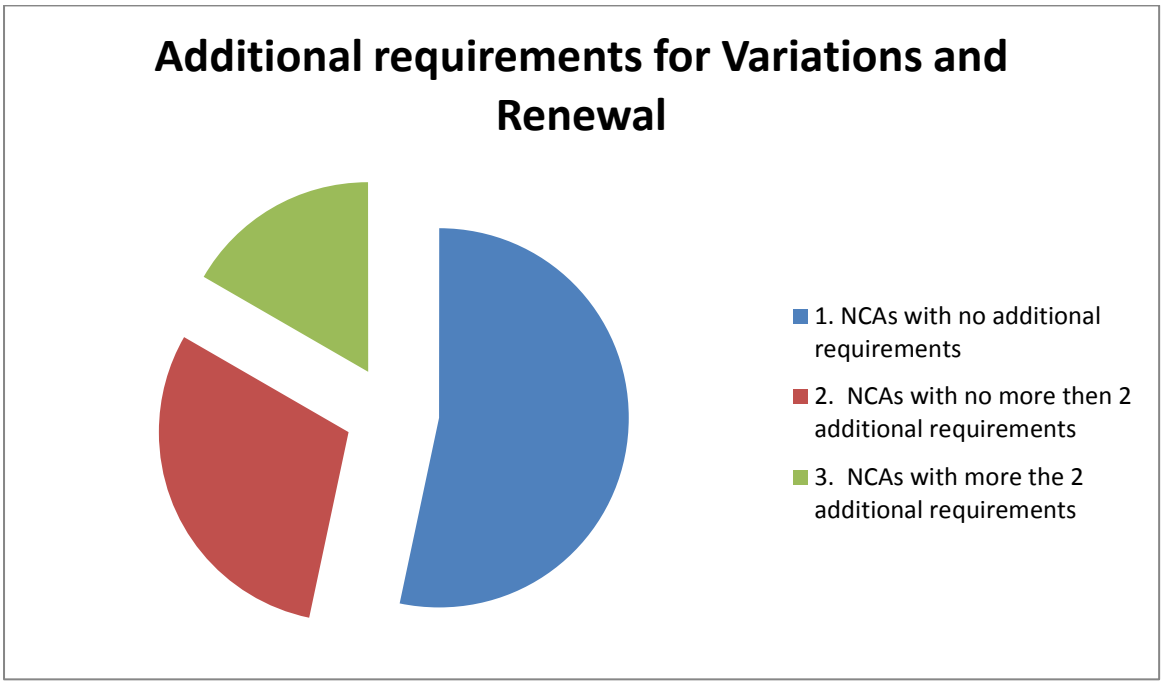

Figure 4 Distribution of the number of the National Competent Authorities (NCAs) based on the number of additional requirements for Variations and Renewals

During the discussion within the survey it was found out that

- besides having multiple national requirements, **Poland** is a difficult authority.
- also critical are the NCAs of **Czech Republic, Slovakia** and from the other **East European countries**.
- **Czech Republic** is very strict regarding the requested LoAs, because these documents are checked by the Law Department of the Ministry of Health.

In case of global companies with affiliates in EU MS, specific national requirements are also prepared locally reducing the workload of global regulatory departments.

From the information provided in the last columns of the ***Annexes IV and V*** it is recognizable that besides the CMDh guidelines [27, 28, 31, 37] additional sources (NCAs websites, CESP Contacts and Cortellis Regulatory Database) are necessary to be consulted in order to obtain a complete image on the specific national requirements for dossier preparation. ***Table 11*** and ***Figure 5*** provide an overview of the sources of information that should be consulted in case of new applications, variations and renewals.

- Besides the CMDh sources, additional sources need to be checked, mostly for preparing complete dossiers for new applications, followed by variations and renewals.
- For 7 of the Member States besides the mentioned additional sources, other specific additional requirements have been found during the survey.
- In case of renewal experience based information was not detected.

Table 11 Overview of sources of information for additional requirements for new applications, variations and renewals in MRP/DCP.

Regulatory activity	Additional requirements	Number of NCAs
New Applications	CMDh guidelines	4
	Other sources	25 (BG, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK)
	Experience based	10 (BE, ES, FR, HU, IT, NL. PL, PT, SK, SI)
Variations	CMDh guidelines	21
	Other sources	5 (CY, FR, PT, SK, RO)
	Experience based	4 (BG, EL, LT, PL)
Renewals	CMDh guidelines	25
	Other sources	5 (CY, ES, HR, RO, SI)
	Experience based	0

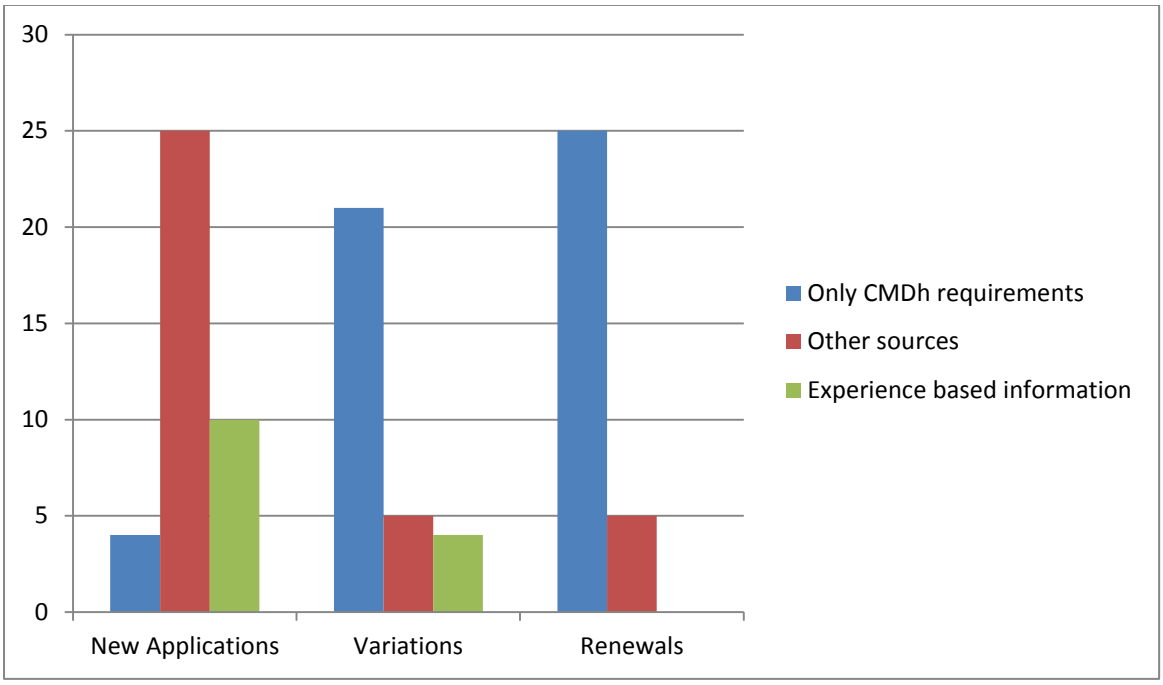

Figure 5 Information sources for the specific additional requirements for New Applications, Variations and Renewals.

15.2. Submission of dossiers via CESP

Submission through CESP is used from most of the national competent authorities as a platform for exchanging regulatory information. Other submission modalities are also possible (see ***Annex IX -*** *Submission modalities*). ***Table 12*** presents the distribution of NCAs that are using the electronic submission platform. ***Figure 6*** shows that CESP submission is brightly used by the majority of NCAs.

Table 12 Particularities for submission via CESP and the number of NCAs concerned.

Particularities for CESP submission	**Countries**	**Number of NCAs**
NCAs using CESP	AT, BE, HR, CY, CZ, DE, DK, EE, ES, FI, IE, IS, LV, LT, LU, MT, NL, NO, PT, RO, SE, SI; UK	23
NCAs still not using CESP	BG, EL, HU, SK	4
NCAs using CESP in a pilot phase	FR, IT, PL	3
	Total	30
National portals to be used (requested or recommended)	ES, DE, IT, PL, UK (SK*)	5 (6*)
NCAs for which additional documentation is to be submitted in paper	CY, CZ, HR, LV, LT, PT, SK	7

*SK is requiring submission of VARs through national portal.

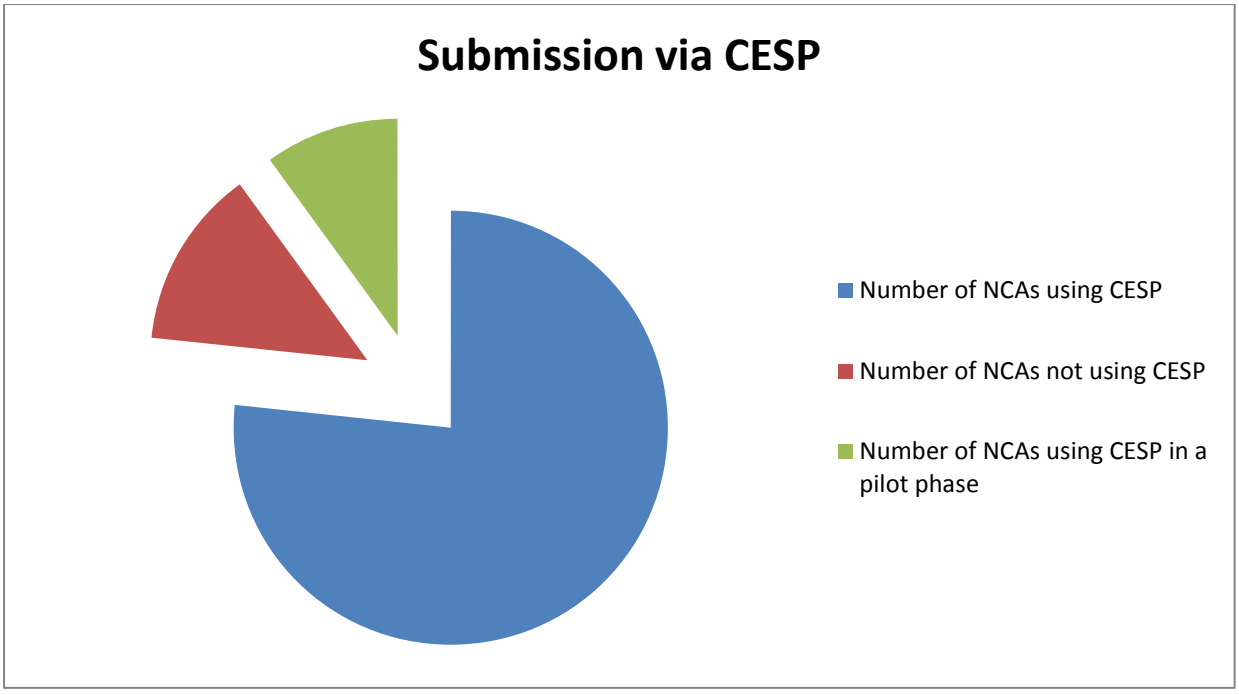

Figure 6 Submission via CESP is used by the majority of the EU NCAs.

15.3. Fees

The fees requested for the submission of the initial applications, renewals and variations are presented in **Annexes VI** – "*Fees for Initial MAAs"*, ***VII*** – "*Fees for Renewals"* and ***VIII*** – "*Fees for MRP Variations"*. Approximated changes have been calculated according to the official rate of 30-May-2015.

The categorization of fees (cost range) was randomly determined, but in such a way that a trend can be recognized in the fees distribution. Evaluations were done only for initial applications and renewals, as the fees for variations are fluctuating depending on the affected medicine products.

In case of variations, is to be mentioned that

- fees are included in the annual fee [AT, NL (except extensions), SE (for type IA and IB)] or
- no fees are requested [LU (all VAR types), MT (when acting as CMS for type IA, IB and II VARs), NO (VARs type IA, IB - if changes in PI are excluded) and UK (type IA VAR)].

Table 13 presents the overview of the fees for **initial applications**: full dossiers and generics.

- The **most expensive countries** when the NCAs are **acting as RMS for full dossiers** are **Malta** (140,000 €) and **United Kingdom** (approx. 200,000 € for DCP and 144,000 € for MRP).
- **Malta** has also higher fees **when acting as RMS for generics** (125,000 €), compared to the same fees in United Kingdom (approx. 26,000 € for DCP and 15,000 € for MRP)
- Malta might have such higher fees when acting as RMS, due to the necessity of the NCA to request external expertise as the Maltese authority is a small one with reduced capacity.

Fees for Romania acting as RMS for full applications are not applicable due to the fact that the NCA is not accepting such applications neither in DCP, nor in MRP.

Comparing the fees for full applications it can be easily recognized (see also ***Annexes VI-VIII*)** that

- the fees for acting as CMS are lower than the ones for acting as RMS, and for full applications lower than for generics.

The majority of NCAs has prices between 10,000 € and 50,000 €, except for acting as CMSs for generics, where the fees for the majority of countries are under 10,000 €. Please refer also to the overview in ***Table 13***.

Table 13 Fees for initial applications. (Fees when acting as CMS are shaded grey).

Fees for initial applications	**Countries**	**Number of countries**
Fees ≤ 10,000 € when acting as RMS for full applications	BG (MRP), CZ (MRP), LT (MRP), LV (MRP), PT	5
Fees between approx.10,000 € and 50,000 € when acting as RMS for full applications	AT, BE, BG (DCP), CY, CZ (DCP), DE (PEI), DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT (DCP), LU, LV (DCP), NO, PL, SI, SK	24
Fees ≥ 50,000 € when acting as RMS for full applications	DE(BfArM), MT, NL, SE, UK	5
Fees ≤ 10,000 € when acting as CMS for full applications	AT, BE, BG, CY, CZ, DK (MRP), EE, FI, HR, HU, IS, LT, LU, LV, MT, RO, SI, SK	18
Fees between approx.10,000 € and 50,000 € when acting as CMS for full applications	DE (BfArM, PEI), DK (DCP), EL, ES, FR, IE, IT, NL, NO, PL, PT, SE	12
Fees ≥ 50,000 € when acting as CMS for full applications	UK	1
Fees ≤ 10,000 € when acting as RMS for generics	BE, BG, CZ, HU, LT, LV (MRP), PT, RO, SK	9
Fees between approx.10,000 € and 50,000 € when acting as RMS for generics	AT, CY, DE, DK, EE, EL, ES, FI, FR, HR, IE, IS, IT, LU, LV (DCP), NL, NO, PL, SE, SI, UK	21
Fees ≥ 50,000 € when acting as RMS for generics	DE (generics with EA - DCP), MT	1
Fees ≤ 10,000 € when acting as CMS for generics	AT, BE, BG, CY, CZ, DE (PEI), DK (MRP), EE, EL (wo BE study), ES, FI, HR, HU, IE; IS, IT, LT, LV, MT, NL (MRP), PL, PT, RO, SE (substances approved in SE), SI, SK, UK (MRP)	27
Fees between approx.10,000 € and 50,000 € when acting as CMS for generics	DE (BfArM), DK (DCP), EL (with BE study), FR, NL (DCP), NO, SE (substances not approved in SE), UK (DCP)	8
Fees ≥ 50,000 € when acting as CMS for generics	none	0

Table 14 presents the overview of the fees for renewals.

- In **Austria, Netherlands, Sweden** no fees are requested for renewals or these are included in the annual fee.
- Other countries do not ask for fees when acting as CMS (Finland, Ireland and United Kingdom).
- United Kingdom presents the higher fee (15,000 €) for renewals when acting as RMS.
- The majority of countries have fees below 10,000 € when acting as RMS or below 5,000 € for being CMS.

Table 14 Fees for Renewal (Fees when acting as CMS are shaded grey).

Fees for Renewal	**Countries**	**Number of countries**
No fees or included in the annual fees	AT; NL; SE	3
Fees not available	LU; LI	2
No fees when acting as CMS	FI; IE; UK	3
Minimal fees (approx. 1000 €) when acting as CMS	CY; EE; IS; LT; MT	5
Fees ≤ 5,000 € when acting as CMS	BE; BG; CZ; DE; DK; ES; FR; HR; HU; IT; LV; PL; PT;RO;SI; SK	16
Fees > 5,000 € when acting as CMS	EL; NO	2
Minimal fees (approx.1000 €) when acting as RMS	IE; MT	2
Fees ≤ 10,000 € when acting as RMS	BE; BG; CY; CZ; DE; DK, EE, EL; ES, FI, FR, HR; HU; IS; IT; LT; LV; NO; PL; PT; RO; SK	22
Fees >10,000 € when acting as RMS	SI; UK	2

15.4. Timelines for obtaining national approvals

Time for granting the national marketing authorizations should be within 30 days after RMS is closing the procedure [19]. Based on practical experience only few countries are really keeping this deadline. The information about these timelines obtained from the survey, is

based on practical data from an initial application of a medicinal product in DCP and from Type II VARs. The timelines after RMS positively closed the procedure are presented in ***Annex X*** – *"Timelines for granting national marketing authorizations and national approvals for Type II variations"*. The evaluations are presented in ***Tables 15*** and ***16*** and ***Figure 7***.

- Only few of the MS (10%) are keeping the indicating timelines for granting the national marketing authorisations.

This fact was stated also in another survey, the Escher report: "Improving the EU system for marketing authorization of medicines" [2] done between 2009 and 2013 on 50 MRP/DCP procedures, where only 7% of the Member States are granting approvals in the legal timeframe.

Table 15. Timelines between the closing of procedure and granting national authorizations

Timelines for granting national authorization	**Countries**	**Number of NCAs**
Within 1 month (30 days)	LT, NL, UK	3
1 – 2 months	BE, CZ, DK, DE, EE, HR, HU, IE, IS, MT, NO, PT, SE	13
2 – 3 months	AT, ES, FI, LV, SI	5
3 – 4 months	FR, IT, LU, PL, SK	5
More than 4 months	BG, CY, EL, RO,	4
	Total	30

Table 16 Timelines for granting national approvals for Type II VARs.

Timelines for granting national approvals for Type II VARs	**Countries**	**Number of NCAs**
Information not available	BG,CY, LU, MT	4
Within 1 month (30 days)	BE, HR, PT	3
1 – 2 months	UK	1
2 – 3 months	AT, CZ, EE, FI,DE, HU, LV, NL,NO, SK, SI, SE	12
3 – 4 months	DK, FR,	2
More than 4 months	EL, IS; IE, IT, LT, PL, RO, ES	8
	Total	30

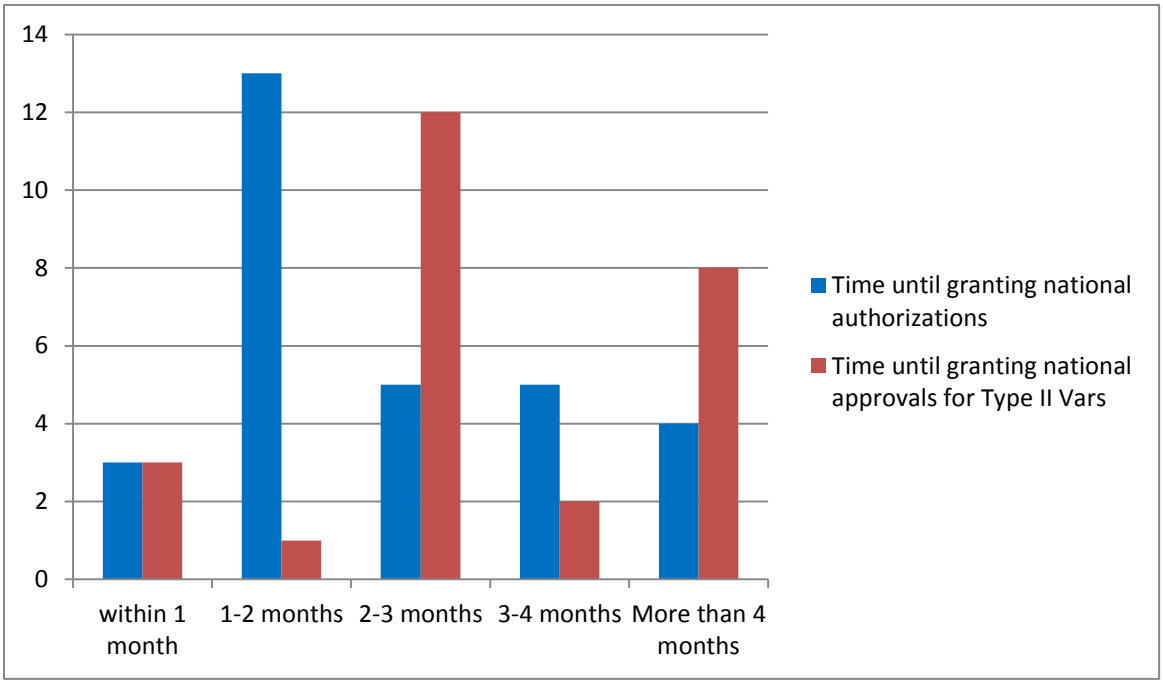

Figure 7 Time until granting national authorizations

The data from **survey** presented in ***Figure 7*** shows that

- most of the NCAs (43%) are granting the national authorizations **within 2 months** or within 3 months in case of type II VARs (46%).

In the Escher report [2]

- most of the national approvals were granted **after more than 4 months**.

The evaluation done in this thesis, based on data from a current survey (end of 2014 and beginning of 2015), might indicate that the NCAs have considerably improved their timelines for granting the national MAs.

15.5. Choosing the RMS

Choosing the RMS is an important aspect that is to be taken into consideration when initiating a new submission of a medicinal product. The scientific expertise of the respective national authority is the main driver in choosing the RMS. The good communication with the Competent Authority of the respective Member State, but also some other aspects already

discussed in this thesis as for example timely evaluation of the dossiers, less complicated additional requirements, the possibility to supply the dossier in electronic format via CESP might be additional reasons to choose the RMS.

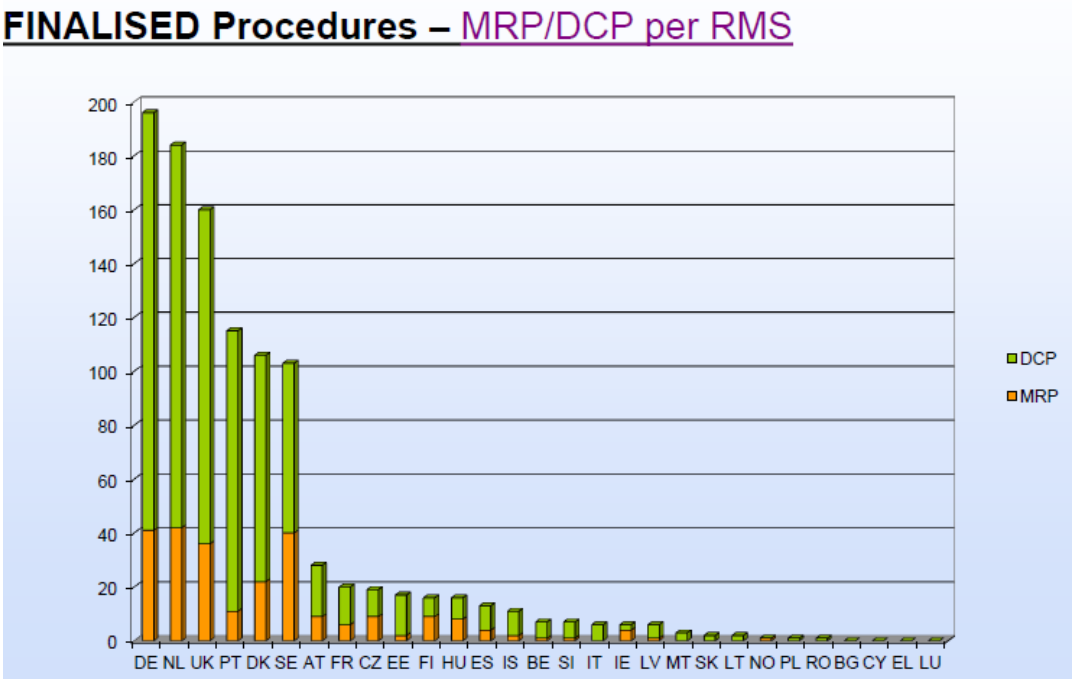

Figure 8 Finalized procedures in 2014 with the indicated countries as RMS, according to [22].

The statistic evaluation done in 2014 by CMDh (***Figure 8***) is showing the finalized MR/DC procedures with the respective MS as RMS.

- This indicates that between the most chosen RMS are Germany, Netherlands, United Kingdom, Portugal, Denmark and Sweden.

16. Conclusions and outlook

Preparing the complete documentation for submission through Mutual Recognition and Decentralised Procedures is a very difficult task for the applicant. Due to the complexity of the requirements that are to be considered timely planning and follow-up are strongly recommended. Even though due to the continuous change of the regulatory environment certain flexibility and adaptation to new and more challenging requirements is to be taken into consideration.

From the above presented collected information it is recognizable that each national competent authority has different specific requirements that are not very easy to be found. The important information that is available on the NCAs websites is often not completely translated in English and only available in the national languages. The Cortellis Regulatory Database is a very important source of information, unfortunately a costly intensive matter that must be brought in via regulatory activities and the turnover of the respective company. Nevertheless also in this database there are still documents available only in national language (e.g. Medical Law of Netherlands IDRAC 64988).

Another vulnerable area in the availability of regulatory requirements is that the information is found contradictory when two different sources are consulted or requested from one side, but not from the other, situation that is sometimes really confusing: For example, in Spain according to IDRAC 5211 submission of REN through CESP is not possible, but this information is not posted on the CESP website. Another example is for UK where according to IDRAC 39066 submission of applications through MHRA portal is required, but according to CMDh guidelines [31, 37] this is not necessary. In addition, in the mentioned guidelines [31, 37] a mistake was made regarding possibility of submission via CESP of new applications, variations and renewals in Greece. This information is not confirmed by the CESP Contact website [66].

The gathered specific additional requirements for Croatia, the most recent EU Member State and the other Eastern European Member States (Bulgaria, Romania, Slovakia, Poland) are really extensive. According to the discussions during the survey these NCAs are also difficult to deal with and late in their evaluations. In order to harmonize the EU requirements also at the national level it is strongly recommended for these MS to reduce their additional requirements and speed up the evaluation time for granting national approvals.

Some additional data requested by the NCAs are not really bringing additional gains for the respective countries as these requirements are mostly related to:

- the signatures of different LoAs, Cover Letters and Application Forms,
- Cover Letters and Application Forms in local languages and originally signed, or
- original signatures and certifications for other statements and declarations.

Aiming to have **harmonized requirements for a single market in the European Union** it is strongly recommended that the NCAs are discussing and agreeing upon reducing additional demands by:

- abandoning the request of providing AF, CL or other declarations in national languages and
- requiring a standard LoA covering all necessary communication aspects and accepting copy of documents without further certifications.

Another proposed solution, in order to reduce the burden for applicant in preparation of the applications and make the requirements more transparent for all involved parties might be that CMDh will prepare a **publicly available database with all the specific requirements** from additional requirements to modalities of submissions and will keep this up to date. All MS should provide input to this database and assure that only the indicated requirements will be required for further submissions. Such a database will speed up the evaluation of the application and the quick delivery of the medicaments to the patients.

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67. The Drug Information Portal of the Bund (Federal Government) and the Laender (States) https://www.pharmnet-bund.de/dynamic/en/index.html (last visited 21.06.2015);

68. "Online Variations unter PharmNet.Bund"-Presentation MDRA 15, Module 6, page 32;

69. MHRA portal https://www.gov.uk/mhra-portal-register-to-submit-forms#use-the-portal-for-applications (last visited 21.06.2015);

70. AEMPS Online Services https://sede.aemps.gob.es/en/home.htm (last visited 21.06.2015);

71. INFARMED Portal http://www.infarmed.pt/pt/medicamentos/uso_humano/redirect.html (last visited 21.06.2015);

72. AIFA Portale Variazione User Manual How to submit a variation type I and type II, http://www.agenziafarmaco.gov.it/sites/default/files/Portale_Variazioni-English_User_Manual051013.pdf (last visited 04.05.2015);

73. AIFA New Information Systems: http://www.agenziafarmaco.gov.it/en/content/aifa-new-information-systems (last visited 21.06.2015);

74. SUKL Portal; https://portal.sukl.sk/evarsym/index.php (last visited 21.06.2015);

75. European Medicines Regulatory Network eSubmission Roadmap, version 1.0, October 2014, http://esubmission.ema.europa.eu/tiges/docs/eSubmission%20Roadmap%20v%201%200_Nov%202014_final_adopted.doc (last visited 21.06.2015);

76. Transition to a compulsory usage of the eAFs for Human and Veterinary Procedures, January 2015; http://esubmission.ema.europa.eu/eaf/docs/eAF%20communication%20-%201%20pager%20-%2017.02.15.pdf (last visited 21.06.2015);

77. Notice to applicants, Volume 2A – Procedures for marketing authorisation – Chapter 1 - Marketing Authorisation, June 2013, http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap1_2013-06_en.pdf (last visited 5.05.2015).

18. Annexes

Annex I - Mutual Recognition Procedure versus Decentralised Procedure

- points in time according to CMDh flow chart for the MRP [20] and CMDh Flow Chart of the Decentralized Procedure [21].

Points in time	Mutual recognition procedure	Points in time	Decentralized Procedure
	First application in one of the MS		
	1st MA granted		
Day -90	RMS to update the Assessment Report	Before Day -14	Starting discussions with RMS.
Day -14	Submission of the dossier to the CMSs. Assessment Report and labeling (SPC+PIL) is circulated from the RMS to the CMS. Validation of application.	Day -14	Simultaneous submission of dossier to the RMS and CMSs Validation of application
Day 0	Procedure start	Day 0	Procedure start
Day 50	CMS to send comments to RMS and the applicant		
Day 60	Responses are sent by the applicant to RMS and CMSs		
Until Day 68	RMS assessment to the applicant responses to be sent to CMSs.		
		Day 70	RMS forward the PrAR to the CMSs and the applicant
Day 75	RMS and the applicant will receive the remaining comments from the applicant. Break-out session between day 73 and 80		
Day 90	CMSs notify RMS and applicant of final position. If consensus is reached, RMS closes the procedure. In case of disagreement, the issues will be sent by RMS to CMDh within 7 days		
		Until Day 100	CMSs send their comments to the RMS, the other CMSs and the applicant

		Until Day 105	Consultation between RMS, CMSs and the applicant. Clock-stop if consensus not reached
		Clock-off period (3 months and if necessary another 3 month)	Applicant prepares and send the responses to the list of questions to the RMS and CMSs.
		Day 106	Restart of the procedure by RMS in case of valid responses to questions.
		Day 120 (Day 0)	DAR is circulated by RMS to the CMSs and applicant.
		Day 145	CMSs send their comments to the RMS, the other CMSs and the applicant
Day 150	The procedures referred to CMDh will be closed by RMS if consensus is reached. In case of disagreement at the CMDh level, RMS refers the matter to CHMP for arbitration.	Day 150	Close of procedure if consensus reached
		Until Day 180	In case of disagreement, RMS communicates the outstanding issues with the applicant and sends a short report to CMSs and the applicant.
		Day 195 (at the latest)	In order to reach consensus, break-out session at EMA with all involved MSs
		Between Day 195 and Day 210	Consultation between RMS, CMSs and the applicant to discuss remaining open issues.
		Day 210 at the latest	Close of procedure if consensus reached. CMSs approve AR, SmPC, labelling and PIL. If consensus not reached, referral to CMDh.
		Day 270 at the latest	Final position adopted by CMDh with possible referral to CHMP in case of disagreement
5 days after close of procedure	Sending of the national translations of SmPC, PIL and labeling to RMS and	5 days after close of procedure	Sending of the national translations of SmPC, PIL and labeling to RMS and CMSs

	CMSs.		
30 days after close of procedure	Granting of national marketing authorizations	30 days after close of procedure	Granting of national marketing authorizations in RMS and CMSs if outcome is positive and no referral to CMDh
		30 days after close of CMDh referral procedure	Granting of national marketing authorizations in RMS and CMSs if positive conclusions by CMDh and no referral to CHMP

Annex II - List of National Competent Authorities of the European Union including Iceland, Lichtenstein and Norway with official name, currency and respective homepage (English versions were indicated. For Lichtenstein and Luxembourg only homepages in national language have been found).

Country	Official name of NCA	Homepage
Austria (AT):	Austrian Medicines and Medical Devices Agency (AGES)	http://www.basg.gv.at/en/basg-austrian-federal-office-for-safety-in-health-care/
Belgium (BE)	Federal Agency for Medicines and Health Products (FAMHP)	http://www.fagg-afmps.be/en/
Bulgaria (BG)	Bulgarian Drug Agency (BDA)	http://en.bda.bg/
Croatia (HR)	Agency for Medicinal Products and Medical Devices of Croatia (HALMED)	http://www.almp.hr/?ln=en
Cyprus (CY)	Ministry of Health, Pharmaceutical Services	http://www.moh.gov.cy/moh/phs/phs.nsf/dmlindex_en/dmlindex_en?opendocument
Czech Republic (CZ)	State Institute for Drug Control (SUKL)	http://www.sukl.eu/index.php?lang=2
Denmark (DK)	Danish Health and Medicines Authorities (sundhedsstyrelsen)	http://sundhedsstyrelsen.dk/en
Estonia (EE)	State Agency of Medicines (SAM), Republic of Estonia	http://www.sam.ee/en
Finland (FI)	Finish Medicines Agency (FIMEA)	http://www.fimea.fi/frontpage
France (FR)	French Agency for the Safety of Health Products (ANSM)	http://ansm.sante.fr/Mediatheque/Publications/Information-in-English
Germany (DE)	The Federal Institute for Drugs and Medical Devices (BfArM)	http://www.bfarm.de/EN/Home/home_node.html
Greece (EL)	National Organization for Medicines (EOF)	http://www.eof.gr/web/guest/home
Hungary (HU)	National Institute of Pharmacy (OGYI)	http://www.ogyi.hu/main_page
Iceland (IS)	Icelandic Medicines Agency (IMA)	http://www.ima.is/
Ireland (IE)	Health Products Regulatory Authority (HPRA)	http://www.hpra.ie/
Italy (IT)	Italian Medicines Agency (Agenzia Italiana del Farmaco - AIFA)	http://www.agenziafarmaco.gov.it/en
Latvia (LV)	State Agency of Medicines of the Republic of Latvia (SAM)	http://www.zva.gov.lv/index.php?setlang=en&large=
Liechtenstein (LI)	Office of Health, Department of Pharmaceuticals	http://www.llv.li/
Lithuania (LT)	State Medicines Control Agency (SMCA)	http://www.vvkt.lt/lit/English/16

Country	Official name of NCA	Homepage
Luxembourg (LU)	Ministry of Health/ Health Directorate	http://www.ms.public.lu/fr/
Malta (MT)	Medicines Authority	http://www.medicinesauthority.gov.mt/home?l=1
Netherlands (NL)	Medicines Evaluation Board (MEB)	http://www.cbg-meb.nl/cbg/en/default.htm
Norway (NO)	Norwegian Medicines Agency (NoMA)	http://www.legemiddelverket.no/English/about-norwegian-medicines-agency/Sider/default.aspx
Poland (PL)	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL)	http://en.urpl.gov.pl/general-information
Portugal (PT)	National Authority of Medicines and Health Products, IP (INFARMED)	http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH
Romania (RO)	National Agency for Medicines and Medical Devices (ANMDM)	http://www.anm.ro/anmdm/en/index.html
Slovakia (SK)	State Institute for Drug Control (SUKL)	http://www.sukl.sk/en?page_id=256
Slovenia (SI)	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP)	http://www.jazmp.si/en/
Spain (ES)	Spanish Agency for Medicines and Health Products (Agencia Espanola de Medicamentos y productos sanitarios AEMPS)	http://www.aemps.gob.es/en/home.htm
Sweden (SE)	Medical Product Agency (LÄKEMEDELSVERKET)	https://www.lakemedelsverket.se/english/
United Kingdom (UK)	Medicines and Healthcare products Regulatory Agency (MHRA)	https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

Annex III - Questions of the survey within the experienced professionals belonging to the company where the author of this master thesis is employed

1. Do you have experience with the national requirements of the NCA during the MRP/DCP procedures? If yes, in which one.
2. When was the last experience you have with the MRP/DCP?
3. What kind of company was the one where you have gathered your experience with the MRP/DCP? (Global acting/ Generic /Innovator/affiliate company)
4. What kind of regulatory activities have you oversee within the MRP/DCP: initial MAA, REN or VARs?
5. For which product type was the MRP/DCP used for? Generic/NCE/NBE?
6. How many NCA were involved?
7. Could you mention the NCA involved?
8. Which NCAs were involved?
9. Have you found out any particular requirements by the preparation of dossiers? Are these different from the CMDh (exact information to be mentioned) requirements published on the CMDh website. Which additional documents were requested?
10. Are any other national requirements that you find out during dossier preparation
11. CESP Submissions: Which NCAs require submitting the initial MAA/REN /VAR beside CESP also through national portals?
12. Timelines for getting the approval. Are there any deviations from the regular timelines? Any experience with this?
13. Do you have any issues or particular issues by paying the fees? Which were these?

Annex IV - National requirements for submission of the initial Marketing Authorisation Application through MRP/DCP

Legend:

	Additional Data from CMDh lists/overviews
	Additional Data from other sources of information (NCAs websites, IDRAC, CESP Contacts)
	Additional Data .- experience based information (survey)

Countries (ISO country codes)	**Additional data /Specific requirements**	**Samples request** (according to CMDh/260/2012)	**Comments**
AT	No additional requirements	On request (FP, AS and non-AS)	
BE	1. Declaration of conformity for national translations of the SmPC, PL and labelling (not as validation issue)	On request (FP, AS and non-AS)	Add Data 1 according to CMDh/043/2007/Rev.09
	2. Filled in Form for Fee with attached proof of payment (in module 1)		Add Data 2 according to IDRAC 5326
	3. Commitment to submit the mock-ups in the national step		Add Data 3 experience based
BG	1. A copy of the contract between MAH and the responsible for batch release/manufacturer/importer/legal representative 2. Pharmacovigilance responsible in Bulgaria 3. PoA (the signatures must be officially authenticated by a notary or an administrative official) 4. Confirmation of an identical dossier with an original signature (if not mentioned in the signed CL). 5. AF, Annex 5.22 with original signature	On request (FP, AS and non-AS)	Add Data 1 to 5 according to CMDh/043/2007/Rev.09
	6. Contact data of a local representative: name, address, telephone, e-mail. 7. Patent declaration and data exclusivity with authentic signature.		Add Data 6+7 according to the NCA website
CY	1. Pharmacovigilance responsible in Cyprus.	On request (FP, AS and non-AS)	Add Data 1 according to CMDh/043/2007/Rev.09
	2. Originally signed application form and cover letter in hard copy must be provided with each submission. 3. Proof of payment		Add Data 2 according to information on CESP website Add Data 3 according to IDRAC 58458
CZ	1. Annex 5.4 LoA for communication on behalf of the applicant/MAH (the signatures must be officially authenticated by a notary or an administrative official). PoA and LoA only requested if SUKL does not have the originals of the general version.	Yes One sample of a medicinal product from each type of immediate packaging should be	Add Data 1 according to CMDh/043/2007/Rev.09

Countries (ISO country codes)	Additional data /Specific requirements	Samples request (according to CMDh/260/2012)	Comments
	2. Proof of Payment (payment forms for administration fee and for reimbursement of expert services in paper)	submitted with the MAA or before issue of the decision.	Add Data 2 IDRAC 13931 and14033
	3. A signed copy of the cover letter should be provided in addition to the electronic submission 4. AF: in electronic format and in paper (2x) with original signature of the authorized representative.		Add Data 3 and 4, according to IDRAC 13931 and practical experience
DE	1. Working documents: a copy of Module 2 in MS Word format (in case of RMS)	On request: In sufficient quantity to permit a full assay and the verification of the control methods used by the manufacturer. For biological products, for which PEI is responsible, samples must be supplied at the same time as the submission of the dossier.	Add Data 1 according to CMDh/085/2008/Rev 16
	2. A national procedure number (ENR number= Einreichungsnummer) should be requested prior to submission. 3. The Cover Letter (originally signed) should contain information about the ENR numbers, the ATC code and e-mail address of the contact person 4. An originally signed Application Form for each strengths and pharmaceutical form is required 5. Filling in of the “Marketing Application Form” / “Zulasungsmaske		Add Data 2-4 according to IDRAC 3216 Add Data 5 BfArM website: http://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Zulassung/zulassungsverfahren/DCP/Zulassungsmaske_mit_Ausfuellhinweise_EN.doc?__blob=publicationFile&v=4
DK	1. CL: dated and signed. An identical copy of CL (without signature) must be part of the electronic documentation. 2. Confirmation for eCTD submissions (a form is provided) in case of the first eCTD submission.		Add Data 1-2 according to NCA website: http://sundhedsstyrelsen.dk/en/medicines/regulation/licensing-of-medicines/marketing-authorisation/application-for-marketing-authorisation/guidelines-on-submission-of-electronic-applications.aspx
EE	1. Some documents are to be additionally signed (hand-written, digital and scanned signatures are accepted): Application Form, Letter of Access to ASMF, PoA, Informed consent letter of MAH (if applicable). 2. Annex 1.5 Proof of payment for the state fee	The applicant is not required to submit the sample of the medicinal product with the MA application. One sample has to be presented when the medicinal product is actually launched.	Add Data 1 according to NCA website http://www.ravimiamet.ee/en/requirements-signatures Add Data 2 according to IDRAC 41353

Countries (ISO country codes)	Additional data /Specific requirements	Samples request (according to CMDh/260/2012)	Comments
EL	1. Statement for the MA transfer to local subsidiary 2. Pharmacovigilance responsible in Greece 3. The trade mark of the product is to be submitted with the new application 4. Working documents: a copy of Module 2 in MS Word format (in case of RMS);	On request (FP, AS and non-AS)	Add Data 1-3 according to CMDh /043/2007/Rev.09 Add data 1 according to CMDh/085/2008/Rev 16
	5. Hard copies are required for M 1-3.; 6. Proof of payment		Add Data 5 on NCA website: http://www.eof.gr/web/guest/procedures Add Data 6 according to IDRAC 28509
ES	1. National Data Base (RAEFAR) should be completed	On request (FP, AS and non-AS)	Add Data 1 according to CMDh /043/2007/Rev.09 and IDRAC 3196
	2. Application Form in Spanish, dully signed 3. Proof of payment		Add Data 2 IDRAC 3196 Add Data 3 IDRAC 595
	4. Specific Cover Letter in Spanish 5. Commitment to submit the mock-ups in the national step.		Add Data 4 and 5 experience based
FI	1. Statement for the MA transfer to local subsidiary	On request (FP, AS and non-AS): FI is not mentioned in the CMDh/260/2012	Add Data 1 according to CMDh/043/2007/Rev.09
	2. Confirmation for electronic submission (in case of first use) 3. Signed cover letter as a PDF file and in paper format (original or a printout copy) 4. Signed AF as an eAF or PDF file and in paper format (original or a printout copy) 5. Technical validation report as PDF file or in paper 6. Proof of payment as a PDF file or in paper		Add Data 2-6 according to NCA website http://www.fimea.fi/marketing_auth/application_procedure_and_documentation/electronic_submissions
FR	1. The person responsible for placing the product on the market in France (so called “exploitant” in French) should be specified (should be a pharmaceutical site)	On request (finished medicinal product, active substances, non-pharmacopoeial active substances and non active substances)	Add Data 1 according to CMDh/043/2007/Rev.09
	2. Original cover letter 3. IDENTIFICATION FORM to fill and append to any correspondence or submission in the context of MA 4. Proof of payment with the “Receipt Deposit Slip” filled in. 5. Electronic submission form (NeeS and eCTD submission forms)		Add Data 2-5 according to IDRAC 39089
	6. Proof of establishment 7. LoA by the responsible person of the applicant to the person responsible for submission of application, signing the application form and communication on behalf of the applicant during the procedure		Add Data 6-7 experience based information

Countries (ISO country codes)	Additional data /Specific requirements	Samples request (according to CMDh/260/2012)	Comments
HR	1. A copy of the contract between future MAH or the applicant and manufacturer responsible for batch release (in case they are not the same entity)—English or Croatian translation. 2. Proof that the future MAH has a QPPV seated in Croatia authorized by the Agency or proof that application for QPPV has been submitted to the Agency 3. Copy of proof of establishment of the applicant (also of the future MAH, in case these two are not the same legal entity) in the EEA (updated extract from the register of entrepreneurs)—not older than 6 months, English or Croatian translation. 4. Annex 5.4 LoA for communication on behalf of the applicant/MAH (original or certified copy): LoAs by the responsible person of the applicant to the person responsible for submission of application, signing the application form and communication on behalf of the applicant a) during the procedure and b) after authorization 5. Annex 5.4 LoA by the responsible person of the future MAH to the applicant (in case these two are not the same legal entity)—original or certified copy. 6. Cover Letter in Croatian with original signature (to be submitted separately for each dose and pharmaceutical form) 7. Written statement by the future MAH (if not seated in Croatia) naming its local representative seated in Croatia with the contract details	On request (finished medicinal product, active substances, non-pharmacopoeial and active substances)	Add Data 8 according to NCA website
	8. Proof of payment of administrative and procedure fees		Add Data 8 according to NCA website
HU	1. Annex 5.4 LoA for communication on behalf of the applicant/MAH (the signatures must be officially authenticated by a notary or an administrative official). Power of attorney – local agent for service of process 2. Confirmation of an identical dossier with an original signature (if not mentioned in the signed CL) 3. Declaration of patent and data exclusivity 4. Cover Letter with original signature 5. AF, Annex 5.22 with original signature; 6. Sample of finish product and API before day 0	Samples of the medicinal product(s), active substance(s) and commercially not available reference material(s) should accompany the Application. The amount of samples should allow three full analysis.	Add Data 1 -6 according to CMDh /043/2007/Rev.09
	7. Proof of payment 8. M 1.3 PI texts in MS Word 9. Module1.3.2 colored mock-up 10. Module1.3.4 readability test/bridging report		Add Data 7-10 according to the NCA website http://www.ogyi.hu/page.php?item=394
	11. Braille-declaration of Text (brand name) about what is going to be print into the folding box		Add Data 11 –experience based information

Countries (ISO country codes)	Additional data /Specific requirements	Samples request (according to CMDh/260/2012)	Comments
IE	1. Fee Application Form is to be filled 2. Proof of payment 3. Additional information for electronic submission: • Technical validation report (name and version of the validation software) • Tracking table for eCTD sequences • Statement of the use of virus-checker (name and version of the anti-virus program) 4. Label, leaflet and label-leaflet mock-ups for marketed presentations must be submitted as a set of consolidated PDF documents for all pack sizes and presentations of the product.	On request (finished medicinal product, active substances, non-pharmacopoeial and non-active substances)	Add Data 1-2 according to NCA website (http://www.hpra.ie/docs/default-source/publications-forms/forms-applications/fin-f0018-fee-application-form-for-human-products-2015-v19.xlsx?sfvrsn=14) and IDRAC 174403 Add Data 3-4 according to NCA website http://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/aut-g0058-guide-to-electronic-submissions---human-medicines-v9.pdf?Status=Master&sfvrsn=16
IS	No additional requirements	On request (finished medicinal product, active substances, non-pharmacopoeial and non-active substances)	
IT	1. Application Form signed by the MAH of the medicinal product in the RMS; 2. When Italy acts as RMS, all annexes to the AF and Statements must be submitted in original or as legalized copy	On request (finished medicinal product)	Add Data 1-2 according to CMDh/043/2007/Rev.09
	3. When Italy acts as CMS only originally signed Application Form and Cover Letter should be submitted together with the CD/DVD 4. Additional forms to be filed in when IT acts as RMS (FORM_AIFA.RMS and Mod. 309_02) 5. Proof of Payment		Add Data 3 according to http://cesp.hma.eu/Contacts Add Data 4 according to NCA website: http://www.agenziafarmaco.gov.it/sites/default/files/how_submit_request_RMS_procedure_0.pdf Add Data 5 IDRAC 3234
	6. Identically statement of the dossier originally signed by the applicant in RMS.		Add Data 6 practical experience
LI	"MAs granted by Austria can be used by Liechtenstein, provided the applicants have identified Liechtenstein as CMS in the application form submitted with MRP or DCP applications. At the end of the procedures, Austria will grant authorisations that will be recognised by Liechtenstein. This marketing authorization can be considered as a marketing authorisation granted in accordance with the pharmaceutical acquis for the purpose of EU legislation and in particular can be considered as a starting point for the purposes of data exclusivity/market protection in the EU." (Notice to Applicants, Vol. 2A, Chapter 1)		

Countries (ISO country codes)	Additional data /Specific requirements	Samples request (according to CMDh/260/2012)	Comments
LT	1. A certified copy of the MA granted by the RMS; 2. An original or certified copy of the contract between MAH and the responsible for batch release/manufacturer/importer/legal representative 3. Annex 5.4 Originally signed LoA for communication on behalf of the applicant/MAH (the signatures must be officially authenticated by a notary or an administrative official); 4. Confirmation of an identical dossier with an original signature 5. AF, Annex 5.22 with original signature 6. All documents should be in Lithuanian or English copies and translations of the documents (proof of establishments , manufacturing authorisations, GMP certificates) should be legalized (notarized or certified)	On request (finished medicinal product, active substances, non-pharmacopoeial and non-active substances)	Add Data 1-6 according to CMDh/043/2007/Rev.09
	7. Signed proof of payment. In cases when payment for multiple applications was made, detailed explanation must be attached. 8. Technical validation report including validation date, time and validation tool		Add Data 7 according to http://cesp.hma.eu/Contacts and IDRAC 42031 Add Data 8 according to NCA website: http://www.vvkt.lt/eng/could-be-find-here/686
LU	1. Filled in Formulaire d'AMM (for CESP-submissions) 2. Cover Letter indicating CESP number 3. Proof of Payment (indicating the procedure number)	On request	Add Data 1-2 according to http://cesp.hma.eu/Contacts Add Data 3 according to NCA website http://www.ms.public.lu/fr/activites/pharmacie-medicament/mise-marche-medic-humain/mise-sur-marche-h/infotaxe_en_maj2013.pdf
LV	1. Confirmation of an identical dossier with an original signature (if not mentioned in the cover letter)	On request (finished medicinal product, active substances, non-pharmacopoeial and non-active substances)	Add Data 1 according to CMDh/043/2007/Rev.09
	2. A signed cover letter indicating CESP number, 3. A signed AF 4. PoA if not previously submitted 5. A copy of SAM invoice and a payment confirmation containing the number of the invoice issued by the Agency		Add Data 2-5 according to http://cesp.hma.eu/Contacts and NCA website http://www.zva.gov.lv//?rel=1756

Countries (ISO country codes)	Additional data /Specific requirements	Samples request (according to CMDh/260/2012)	Comments
MT	1. Specimens should be included in the application if MT is RMS	Product samples to be submitted at start of procedure if MT is RMS. If MT is CMS by request (finished medicinal product, active substances, non-pharmacopoeial and non-active substances)	Add Data 1 according to CMDh/260/2012, Rev 2
	2. Cover letter (paper copy only required with CD/DVD/paper submission) 3. Module 1.3.1 product information – in editable word version, clean and track changed if applicable 4. Proof of payment		Add Data 2-3 according to NCA website: http://www.medicinesauthority.gov.mt/file.aspx?f=744 Add Data 4 according to IDRAC 44263
NL	1. CL of an electronic dossier must contain the following additional information: RVG (Dutch license) numbers, case numbers (Dutch: zaaknummer), the number of CD(s)/DVD(s) for the complete dossier; a statement that the content of the electronically submitted information is identical to that of the corresponding parts as hard copy; a statement that the submission has been checked with an up-to-date virus	On request (finished medicinal product and active substances)	Add Data1- according to IDRAC 3178
	2. Proof of establishment		Add Data 2 experience based
NO	Price application form for each new pharmaceutical form, strength or size	On request (finished medicinal product and active substances)	Add Data according to the NCA website: http://www.legemiddelverket.no/English/price_and_reimbursement/price-application/Sider/default.aspx
PL	1. Original or copy signed by Notary Public of updated extract from the register of entrepreneurs for proposed MAH for Poland (max. 6 months) 2. Proof that the applicant and proposed MAH in Poland are taken as one entity according to commission communication 98/C 229/03 (original) 3. Annex5.4 LoA for communication on behalf of the applicant (the signatures must be officially authenticated by a notary or an administrative official) 4. AF, Annex 5.22 with original signature	Samples (finished medicinal product, active substances, non-pharmacopoeial and non-active substances) should be submitted upon the request of Competent Authority in quantity and time indicated in request (usually the quantity should be sufficient amount to permit a full assay and the verification of control	Add Data 1-4 according to CMDh/043/2007/Rev.09

Countries (ISO country codes)	Additional data /Specific requirements	Samples request (according to CMDh/260/2012)	Comments
	5. Cover Letter providing an exact description of the content and the previously submitted sequences. 6. Proof of payment Additional documents to be submitted in paper: 7. Letter of Access to ASMF sent together with the restricted part of ASMF 8. Informed consent letter of MAH of authorized product 9. A written confirmation from the API manufacturer to inform the MAH in case of modification of the manufacturing process or specifications 10. A statement from the QP of the MAH in Section 2.5.1 and from the QP of each of MAHs (i.e. located in EEA) listed in section 2.5.2 where the active substance is used as a starting material that the active substance manufacturer(s) referred to in Section 2.5.3 operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. 11. Declaration of an identical dossier. 12. Declaration form for submission of DDPS Paper submission in case PL is RMS: 13. MAs of a medicinal products in the country/countries of manufacturing if not available EudraGMP 14. A statement or, when available, a certificate of GMP compliance, not older than 3 years for the manufacturer(s) of the medicinal product issued by an EEA competent authority or MRA partner authority 15. Module 1.4 – Information about the experts – Quality, Non-Clinical and Clinical 16. A copy of the authorization of the Minister competent for the environment for marketing a GMO product, or a written commitment to submit such a document; 17. A copy of consent of the minister competent for the environment for restricted use of GMO or deliberate release of GMO into the environment; 18. In case of clinical trials carried out outside the territory of the EU MS or the MS of the European Free Trade Association- a statement that those trials meet the ethical conditions defined in the provisions of Chapter 2a(if applicable)	methods used by the manufacturer)	Add Data 5 according to the NCA website: http://en.urpl.gov.pl/system/files/Downloads/20120921152526/Guidance_for_Marketing_Authorization_Holders_on_Submitting_Documents_in_Electronic_Format.pdf?1348233966 Add Data 6 according to IDRAC 14857 Add Data 7-18 according to the NCA website: http://en.urpl.gov.pl/system/files/Downloads/20120921152526/Table_1.pdf?1348233967
	19. Translation of the RMP in national language (occasionally requested)		Add Data 19experience based information
PT	1. Originally signed AF 2. Originally signed Cover Letter 3. Proof of payment. 4. Declaration form for the use of e-mail communications with Infarmed	On request (finished medicinal product, active substances, non-pharmacopoeial and non-active substances)	Add Data 1-3 according to http://cesp.hma.eu/Contacts Add Data 4 according to NCA website http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH/SUBMISSION_MARKETING_AUT_APPLICATION

Countries (ISO country codes)	Additional data /Specific requirements	Samples request (according to CMDh/260/2012)	Comments
	5. In case PT is RMS, specific request form to be filled in for MRP (CMDh common form for DCP)		Add Data 5 according to NCA website: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/AUTORIZACAO_DE_INTRODUCAO_NO_MERCADO/PORTUGAL_COMO_ESTADO_MEMBRO_DE_REFERENCIA
	6. Proof of establishment		Add data 6 experience based information
RO	1. Annex5.4 LoA for communication on behalf of the applicant (the signatures must be officially authenticated by a notary or administrative official); 2. Confirmation of the identical dossier with an original signature (if not mentioned in the signed CL). 3. AF, Annex 5.22 with original signature	On request (finished medicinal product)	Add Data 1-3 according to CMDh/043/2007/Rev.09
	4. Letter of intent for the submission of an application for marketing authorisation 5. Proof of payment (Tax and Tariff Payment Form with RO as RMS or CMS to be filled in)		Add Data 4-5 according to NCA website http://www.anm.ro/anmdm/en/med_formulare.html
SE	1. Working documents: a copy of Module 2 in MS Word format (in case SE is RMS)	On request (in the presentation authorized in the RMS), reference substances, main impurities and main degradation products should be provided within 7 calendar days enough samples for 2 full assays and the method verification.	Add Data 1 according to CMDh/085/2008/Rev 15
	2. A sample of the finished product (or a placebo) in its intended package should accompany the application (no final labelling necessary). MPA checks how patient friendly the intended package is.		Add Data 2 according to NCA website: http://www.lakemedelsverket.se/english/product/Medicinal-products/Practical-guidance-for-submissions-/
SI	1. Cover Letter in Slovenian language signed according to the JAZMP requirements (advanced electronic or "wet-ink" hand signature) 2. Completed application form in English or Slovenian language (as applicable) 3. Proof of payment	On request (finished medicinal product, active substances, non-pharmacopoeial and non-active substances) should be submitted in quantity	Add Data 1 according to: http://cesp.hma.eu/Contacts Add Data 2-3 according to NCA website: http://www.jazmp.si/en/human_medicines/marketing_authorisation/

Countries (ISO country codes)	Additional data /Specific requirements	Samples request (according to CMDh/260/2012)	Comments
	4. Proof of establishment 5. LoA	and time frame indicated in request (sufficient to permit a full assay and the verification of control methods by the manufacturer).	Add Data 4-5 experience based information
SK	1. Statement for the MA transfer to local subsidiary (originally signed) 2. Original or copy signed by notary public of updated extract from the register of entrepreneurs for proposed MAH for Slovakia (not older than 3 years). 3. LoA for communication on behalf of the applicant/MoH (the signatures must be officially authenticated by a notary or administrative official)—Signed by person listed in the extract from the register of entrepreneurs 4. CL in the Slovak language	Samples of MP in the form of final sales presentation and reference substances of AS, main degradation products and main impurities should be provided in quantity sufficient for three full analyses, not requested for MRP/DCP if SK is CMS	Add Data 1-4 according to CMDh/043/2007/Rev.09
	5. 3 copies of AF in English (provided in EC NtA) 6. 3 copies of AF in Slovak (provided by SIDC/SUKL) 7. PoP generated from e-Application system. 8. Copy of GMP certificates and manufacturing authorisations 9. Local representative is required. 10. If SK act as RMS, samples of finished product and reference substances to be submitted with the application		Add Data 5-10 according to the NCA website: http://www.sukl.sk/en/registration-of-medicinal-product/forms-and-instructions/additional-requirements-for-submission-of-the-dossier-in-the-slovak-republic?page_id=1945
	11. Proof of establishment		Add Data 11 experience based information
UK	1. Only MHRA template for SmPC should be used. It should not be altered in any way beyond insertion of information. 2. An amended marketing authorization (MA) application form might be necessary to be filled before issuing of the marketing authorization 3. Proof of payment.	On request (finished medicinal product, active substances, non-pharmacopoeial and non-active substances	Add Data 1 according to IDRAC 39066 Add Data 2 according to IDRAC 75 Add Data 3 according to the NCA website: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/368314/Pre-submission_checklist.pdf and IDRAC 519

Annex V - National requirements for Variations and Renewals

According to CMDh/261/2012, Rev 2 September 2013 samples are requests for the following variations:

a) B.II.a.1 Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking;

b) B.II.a.2 Change in the shape or dimensions of the pharmaceutical form;

c) B.II.a.3 Changes in the compositions (excipients) of the finished product;

d) B.II.e.1 Change in immediate packaging of the finished product;

e) B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging);

f) B.IV.1 Change of a measuring or administration device.

Legend:

	Additional Data from CMDh lists/overviews
	Additional Data from other sources of information (NCAs websites, IDRAC, CESP Contacts)
	Additional Data .- experience based information (survey)

Countries (ISO country codes)	**Additional data /Specific requirements for REN and VARs**	**Samples request**	**Comments**
AT	**VAR+REN:** No deviation from EU requirements	On request for VAR type: a, b, c, e and f	
BE	**VAR+REN:** 1. Filled in Form for fees with attached proof of payment No deviation from EU requirements	On request for VAR type: a, b, c, e and f	Additional Data according to *IDRAC 5326*
BG	**VAR:** 1. Originally signed Application Form 2. Current contact person for Bulgaria on behalf of MAH	On request for VAR type: a, b, c, d, e and f	Add Data 1-2 according to CMDh/197/210/Rev 3
	3. Proof of payment		Add Data 3 experience based information

Countries (ISO country codes)	Additional data /Specific requirements for REN and VARs	Samples request	Comments
	REN: 1. Originally signed Application Form 2. Current contact person for Bulgaria on behalf of MAH 3. Originally signed Declaration from the QP of the MAH responsible for batch release and from the QP of each of the MAH using the API confirming their manufacture in compliance with the GMP		Add Data 1-3 according to CMDh/197/210/Rev 3
	4. Proof of payment		Add Data 4 experience based information
CY	**VAR +REN:** 1. Originally signed application form and cover letter in hard copy must be provided with each submission even if submitted via CESP 2. Proof of payment	On request for VAR type: a, b, c, d, e and f	Add Data 1 according to CESP Contacts Add Data 2 according to IDRAC 58458
CZ	**VAR +REN:** 1. Original version of copy of PoA 2. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents");	Samples should be submitted with the application for VAR type: a, b, c, d, e and f	Add Data 1 according to CMDh/197/210/Rev 3 Add Data 2 according to CMDh/006/2008/Rev 14
	3. Proof of payment		Add Data 3 according to IDRAC 14033
DE	**VAR +REN:** 1. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents") No deviation from EU requirements (IDRAC 5337)	On request for VAR type: a, b, c, e and f (request is mentioned only for PEI).	Add Data 1 according to CMDh/006/2008/Rev 14
DK	**VAR +REN:** 1. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents") No deviation from EU requirements (IDRAC 354)	Not applicable or not mentioned.	Add Data 1 according to CMDh/006/2008/Rev 14
EE	**VAR +REN:** 1. The proof of payment of the state fee (REN- 31.95 EUR and VAR - 15.97 EUR) is to be attached to the applications submitted through MRP No deviation from EU requirements (IDRAC 41350)	On request for VAR type: a, b, c, e and f	Add. Data 1 according to IDRAC 41353
EL	**VAR**: 1. Application Form in National language 2. VAR change of name of product: submission of the product's Trademark 3. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents")	On request for VAR type: a, b, c, e and f	Add Data 1+2 according to CMDh/197/210/Rev 3 Add Data 3 according to CMDh/006/2008/Rev 14

Countries (ISO country codes)	Additional data /Specific requirements for REN and VARs	Samples request	Comments
	4. Proof of payment		Add Data 4 according to IDRAC 28509
	5. Copy of marketing authorization or last renewal; 6. Concise table form summarizing the scope of the variation Type IA/IB (to be written in Greek and sent via e-mail)		Add Data 5-6 experience based information
	REN: 1. Renewal Application Form to be submitted in Greek 2. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents")		Add Data 1 according to CMDh/197/210/Rev 3 Add Data 2 according to CMDh/006/2008/Rev 14
	3. A general information form with the copy of the marketing authorization 4. Proof of Payment		Add Data 3 according to IDRAC 28458 Add Data 4 according to IDRAC 28509
ES	**VAR +REN:** 1. Application Form in national language 2. National Database should be completed 3. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents")	On request for VAR type: a, b, c, d, e and f	Add Data 1-2 according to CMDh/197/210/Rev 3 Add Data 3 according to CMDh/006/2008/Rev 14
	4. Proof of payment together with the filled in payment form		Add Data 4 according to IDRAC 595
FI	**VAR +REN:** 1. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents")	Not applicable or not mentioned	Add Data 2 according to CMDh/006/2008/Rev 14
	2. Proof of payment (for REN -Proof of payment only when FI is acting as RMS, otherwise the fee is included in the annual fee)		Add Data 1 according to IDRAC 26004
FR	**VAR +REN:** 8. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents")	3 samples should be provided with the application for VAR type: a, b, c, e and f	Add Data 1 according to CMDh/006/2008/Rev 14
	9. IDENTIFICATION FORM to fill and append to any correspondence or submission in the context of MA 10. Proof of payment with the "Receipt Deposit Slip" filled in 11. Electronic submission forms (NeeS or eCTD submission form)		Add Data 2-4 according to IDRAC 39089

Countries (ISO country codes)	Additional data /Specific requirements for REN and VARs	Samples request	Comments
HR	**VAR** 1. A copy of the Contract between MAH of the applicant and the manufacturer responsible for batch release (in case they are not the same legal entity and in case manufacturer responsible for batch release site is changed) 2. Proof that MAH has responsible person for Pharmacovigilance seated in HR authorized by the agency 3. Written statement by MAH (if not seated in HR) naming its local representative seated in HR with contact details 4. Cover letter in Croatian for each dose or pharmaceutical form (original or certified copy) 5. Originally signed Application Form 6. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents")	On request for VAR type: a, b, c, e and f	Add Data 1-5 according to CMDh/197/210/Rev 3 Add Data 6 according to CMDh/006/2008/Rev 14
	7. Proof of payments (the administrative fee of 300 HRK and the fee for the procedure)		Add Data 7 according to IDRAC 115257 and 75145
	REN: 1. Annex 5.4 LoAs by the responsible person of the applicant to the person responsible for submission of application, signing the application form and communication on behalf of the applicant a) during the renewal procedure and b) after renewal (original or certified copy) / Each responsible person for communication has to be authorised by the responsible person of the legal entity where he or she is employed. 2. Annex 5.4 LoA by the responsible person of the future MAH to the applicant (in case these two are not the same legal entity)—original or certified copy. 3. A copy of the Contract between MAH of the applicant and the manufacturer responsible for batch release (in case they are not the same legal entity) 4. Written statement by the future MAH (if not seated in Croatia) naming its local representative seated in Croatia with the contract details 5. Cover letter in Croatian for each dose or pharmaceutical form (original or certified copy) 6. Originally signed Application Form 7. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents")		Add Data 1-6 according to CMDh/197/210/Rev 3 Add Data 7 according to CMDh/006/2008/Rev 14

Countries (ISO country codes)	Additional data /Specific requirements for REN and VARs	Samples request	Comments
	8. Proof of payment of the administrative fee and the procedure fee 9. Declaration by the responsible person of the marketing authorization holder in the Republic of Croatia, that at the time of renewal of the marketing authorization in the Republic of Croatia, the product is identical to the product marketed in the Reference Member State (the original document) 10. written responses of marketing authorization holders in the European Union to request for supplementary information from renewal procedure under the MRP or DCP, 11. Submitted/approved documentation in the renewal procedure in the Reference Member State		Add Data 8-11 according to IDRAC 90590
HU	**VAR+REN:** 1. Proof of payment	1 samples should be submitted with the application for VAR type: a, b, c, e and f	Add Data 1 according to IDRAC 14226
IE	**VAR+REN:** 1. Electronic copy of the proposed Product Information in word format with tracked changes MS Word (“working documents”)	On request for VAR type: a, b, c, d, e and f	Add Data 1 according to CMDh/006/2008/Rev 14
	2. Fee Application Form		Add Data 2. IDRAC 174403
IS	**VAR+REN:** 1. Electronic copy of the proposed Product Information in word format with tracked changes MS Word (“working documents”) No deviation from EU requirements (IDRAC 3234)	On request for VAR type: a, b, c, e and f	Add Data 1 according to CMDh/006/2008/Rev 14
IT	**VAR:** 1. All Annexes to the Application Form and Statements must be submitted in original or as legalized copies (national variations and when acting as RMS)	On request for VAR type: a, b, c, e and f	Add Data 1 according to CMDh/197/210/Rev 3
	2. Proof of payment		Add Data 2 according to IDRAC 3234
	REN: 1. All Annexes to the Application Form and Statements must be submitted in original or as legalized copies (when acting as RMS) 2. Original cover page of the PSUR must be submitted in original and signed by the QPPV/EU-QPPV 3. Annex 5.4 LoA for communication on behalf of MAH for contact person signed by the person, whose name is available in proof of establishment of the MAH (original or notarized copy)		Add Data 1-3 according to CMDh/197/210/Rev 3
	4. Proof of payment		Add Data 4 according to IDRAC 3234

Countries (ISO country codes)	Additional data /Specific requirements for REN and VARs	Samples request	Comments
LT	**VAR:** 1. VAR change of name of product: submission of the product's Trademark 2. Original version or copy of the PoA 3. LoA for communication on behalf of MAH for contact person signed by the person, whose name is available in proof of establishment of the MAH (original or notarized copy) 4. Originally signed Application Form 5. LoA for communication on behalf of the applicant/MAH 6. Originally signed cover letter 7. Originally signed proof of payment 8. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents")	On request for VAR type: a, b, c, d, e and f	Add Data 1-7 according to CMDh/197/2010/Rev.3 Add Data 8 according to CMDh/006/2008/Rev 14
	9. Explanation form concerning the payment details		Add Data 9 experienced base information
	REN: 1. Original version or copy of the PoA 2. LoA for communication on behalf of MAH for contact person signed by the person, whose name is available in proof of establishment of the MAH (original or notarized copy) 3. Originally signed Application Form 4. LoA for communication on behalf of the applicant/MAH 5. Originally signed cover letter 6. Originally signed proof of payment 7. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents")		Add Data 1-6 according to CMDh/197/2010/Rev.3 Add Data 7 according to CMDh/006/2008/Rev 14
LU	**VAR+REN:** No deviation from EU requirements		
LV	**VAR+REN:** 1. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents")	On request for VAR type: a, b, c, e and f For REN one sample of the medicinal product and the most recent labeling of the medicinal product (by request of SAM). (IDRAC 40780).	Add Data1 according to CMDh/006/2008/Rev 14
	2. Filled in Payment Application to be submitted before submitting and the copy of SAM invoice is to be included in the application		Add Data according to IDRAC: 40671

Countries (ISO country codes)	Additional data /Specific requirements for REN and VARs	Samples request	Comments
MT	**VAR+REN:** 1. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents")	On request for VAR type: a, b, c, d, e and f	Add Data 1 according to CMDh/006/2008/Rev 14
	2. Proof of payment		Add Data according to IDRAC: 44263
NL	**VAR+REN:** No deviation from EU requirements (IDRAC 3211)	On request for VAR type: a, b, c, e and f	Add Data according to
NO	**VAR+REN**: 1. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents")	On request for VAR type: a, b, c, e and f	Add Data 1 according to CMDh/006/2008/Rev 14
PL	**VAR:** 1. All Annexes to the Application Form and Statements must be submitted in original or as legalized copies (national variations) 2. LoA for communication on behalf of MAH for contact person signed by the person, whose name is available in proof of establishment of the MAH (original or notarized copy) 3. Proof of establishment of the MAH in the EEA (updated extract from the register of entrepreneurs-original document or notarized copy – all details about a company and the members of management). The name of a person who will sign the LoA should be also placed in this document. 4. Originally signed AF 5. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents")	On request for VAR type: a, b, c, d, e and f	Add data 1-4 according to CMDh/197/2010/Rev.3 Add Data 5 according to CMDh/006/2008/Rev 14
	6. Proof of payment		Add Data 6 according to IDRAC 14857
	7. VAR updating the PSMF –signed PSMF summary		Add Data 7 experience based information
	REN: 1. All Annexes to the Application Form and Statements must be submitted in original or as legalized copies (when acting as RMS) 2. LoA for communication on behalf of MAH for contact person signed by the person, whose name is available in proof of establishment of the MAH (original or notarized copy) 3. Proof of establishment of the MAH in the EEA (updated extract from the register of entrepreneurs-original document or notarized copy – all details about a company and the members of management). The name of a person who will sign the LoA should be also placed in this document. 4. Authorized agent for receiving letters resident in PL 5. Originally signed AF 6. Originally signed Declaration from the QP of the MAH responsible for batch release and from the QP of each of the MAH using the API confirming their		Add Data 1-6 according to CMDh/197/2010/Rev.3

Countries (ISO country codes)	Additional data /Specific requirements for REN and VARs	Samples request	Comments
	manufacture in compliance with the GMP 7. Electronic copy of the proposed Product Information in word format with tracked changes MS Word (“working documents”)		Add Data 7 according to CMDh/006/2008/Rev 14
	8. Proof of payment		Add Data 8 according to IDRAC 14857
PT	**VAR+REN:** 1. Electronic copy of the proposed Product Information in word format with tracked changes MS Word (“working documents”)	No applicable or not mentioned	Add Data 1 according to CMDh/006/2008/Rev 14
	2. Originally Signed cover letter and Application Form (without annexes) 3. Proof of fee payment to INFARMED, I.P		Add Data 2+3 according to http://cesp.hma.eu/Contacts
RO	**VAR**: 1. Original version or copy of the PoA 2. VAR type IB no A.2b) variation when the new proposed invented name falls under the case of the “umbrella” brands, information according to chapter II of the Minister of Health Order No.1453/28.12.2005 in support of applications for approval of “umbrella” brands has to be submitted with the application or requested as day 20 comment.	On request for VAR type: a, b, c, e and f	Add data 1-2 according to CMDh/197/2010/Rev.3
	3. Letter of intent for the submission of a variation 4. Proof of Payment (Payment Form Tariff for Variation of a Marketing Authorisation to be filled in)		Add Data 3-4 according to NCA website: http://www.anm.ro/anmdm/en/med_formulare.html
	REN: 1. Original version or copy of the PoA 2. Originally signed Declaration from the QP of the MAH responsible for batch release and from the QP of each of the MAH using the API confirming their manufacture in compliance with the GMP		Add Data 1-2 according to CMDh/197/2010/Rev.3
	3. Proof of Payment (Tax and Tariff Payment Form for Renewal)		Add Data 3 according to NCA website: http://www.anm.ro/anmdm/en/med_formulare.html
SE	**VAR+REN** 1. Electronic copy of the proposed Product Information in word format with tracked changes MS Word (“working documents”)	Not applicable or not mentioned	Add Data 1 according to CMDh/006/2008/Rev 14

Countries (ISO country codes)	Additional data /Specific requirements for REN and VARs	Samples request	Comments
SI	**VAR+REN**: 1. Cover letter in Slovenian language (signed by an advanced electronic signature based on a qualified certificate for electronic signatures or "wet-ink" hand-signed) 2. Electronic copy of the proposed Product Information in word format with tracked changes MS Word ("working documents")	On request for VAR type: a, c, e and f	Add data 1 according to CMDh/197/2010/Rev.3 and http://cesp.hma.eu/Contacts Add Data 2 according to CMDh/006/2008/Rev 14
SK	**VAR:** 1. Application Form in Slovak language 2. Proof of payment	On request for VAR type: **c** and **f** Samples of new container or new dosage form should be submitted with the VAR type a, b and e	Add Data 1 according to NCA website http://www.sukl.sk/en/registration-of-medicinal-product/forms-and-instructions/additional-requirements-for-submission-of-the-dossier-in-the-slovak-republic?page_id=1945 Add Data 2 according to IDRAC 14044
	REN: 1. In addition to the EU AF, a specific application form must be filled in Slovak language and submitted together with the renewal package. 2. Proof of payment		Add Data 1according to IDRAC 14039 Add Data 2 according to IDRAC 14044
UK	**VAR+REN:** 1. Proof of payment (in case of REN only when UK is RMS)	On request for VAR type: a, b, c, e and f	According to IDRAC 519

Annex VI - Fees for Initial MAAs (only first pharmaceutical form and one strength) (General information from IDRAC 55076, 122272, 45589 and 122269; Sources of additional information are mentioned separately for each country in the 1st column).

Approximated changes are given according to the official rate of 30-May-2015.

Countries (ISO country codes)	Modality of payment	DCP RMS	DCP CMS	RMP RMS	RMP CMS
AT (IDRAC 2698)	**Invoice** Fees to be paid by transfer to the account of the Medizinmarktaufsicht/BASG The fees (registration fees and stamp duties) are to be paid on Authority request after submission or after approval.	**New active substance** 50,000 € (esub only) 52,500 € (other sub) **Generic** 37,000 € (esub only) 38,850 € (other sub) Further doublets: 50% fee reduction	**New active substance** 8,560 € (esub only) 8,988 € (other sub) **Generic** 6,800 € (esub only) 7,140 € (other sub) **CMS for Lichtenstein** 1,350 € (esub only) 1,417.50 € (other)	**New active substance** 39,300 € (esub only) 41,265 € (other sub) **Generic** 30,000 € (esub only) 31,500 € (other sub) **Repeat Use Procedure** 6.000 € (esub only) 6.300 € (other sub) Further doublets: 50% fee reduction	**New active substance** 6,800 € (esub only) 7,140 € (other sub) **Generic** 6,800 € (esub only) 7,140€ (other sub) **CMS for Liechtenstein** Simultaneous application in AT 1,350 € (esub only) 3,400 € (other sub) Subsequent application in AT 1,417.50 € (esub only) 3,570 € (other sub)
BE (IDRAC 5326)	**Proof of payment** To be attached to the filled in Form for Fees (in Dutch or French) and submitted in module 1 of the dossier Fees to be paid by bank transfer.	**New active substance** 2x9141.20 € **Generic** 2x4875.30 €	**New active substance** 9141.20 € **Generic** 4875.30 €	**New active substance** 2x9141.20 € **Generic** 2x4875.30 €	**New active substance** 9141.20 € **Generic** 4875.30 €
BG	**Proof of payment** **BGN=** Bulgarian lev	**New active substance** 20,000 **BGN** *(10,222 €)* **Generic** 14,000 **BGN** *(7,156 €)*	**New active substance** 10,000 **BGN** *(5,111 €)* **Generic** 7,000 **BGN** *(3,578 €)*	**New active substance** 16,000 **BGN** *(8,178 €)* **Generic** 12,000 **BGN** *(6,133 €)*	**New active substance** 8,000 **BGN** *(4,089 €)* **Generic** 6,000 **BGN** *(3,067 €)*

Countries (ISO country codes)	Modality of payment	DCP RMS	DCP CMS	RMP RMS	RMP CMS
CY (IDRAC 58458)	**Proof of payment** Proof of payment is to be included in the dossier by the time of submission. Payments may be made via the JCCSMART, through the webpage of Pharmaceutical Services. The first fee is payable with the submission of the application, the second one, of the same amount, is payable with the issue of the Marketing Authorisation.	**New active substance** 13,660 €+ 13,660 € **Generic** 8,540 € +8,540 €	**New active substance** 854 €+ 854 € **Generic** 512 €+ 512 €	**New active substance** 13,660 €+ 13,660 € **Generic** 8,540 € +8,540 €	**New active substance** 854 €+854 € **Generic** 512 € +512 €
CZ (IDRAC 14033)	**Proof of payment** There are 2 different fees to be paid: an administrative and a registration fee. An administrative fee of 2,000 **CZK** (73 EUR) is to be paid by applying for registration. If the application was submitted before 05-Jun-2005, the fee is 300,000 **CZK** (10,932 EUR). **CZK**= Czech Koruna	**New active substance** 390,000 **CZK** *(14,212€)* **Generic** Not available	**New active substance** 110,000 **CZK***(4,008 €)* **Generic** 90,000 **CZK** (3,280 €)	**New active substance** 250,000 **CZK** *(9,110 €)* **Generic** 200,000 **CZK** *(7,288 €)*	**New active substance** 110,000 **CZK** *(4,008 €)* **Generic** 90,000 **CZK** *(3,280* €)
DE (BfArM) (IDRAC 317)	**Invoice** Fees to be paid via bank transfer to the Landeszentralbank Bonn. The appropriate fees have to be paid by the applicant to the authorities within 14 days of receipt of the invoice. EA= Environmental Assessment	**New active substance** 113,900 € (with EA) 98,500 € (without EA) **Generic** 57,000 € (with EA) 41,600 € (without EA)	**New active substance** 21,400 € (with EA) 17,100 € (without EA) **Generic** 18,100 € (with EA) 13,800 € (without EA)	**New active substance** 98,000 € (with EA) 89,300 € (without EA) **Generic** 46,600 € (with EA) 37,900 € (without EA)	**New active substance** 24,100 € (with EA) 19,500 € (without EA) **Generic** 20,500 € (with EA) 15,900 € (without EA)
DE (PEI)	**Invoice** The fees consist of the fee charged by PEI for acting as RMS in the MRP/DCP plus the assessment report fee (AR). The fees depend on the individual product, for difficult cases these may be increased up to twice the fee.	**New active substance and generic** (2,050 – 12,780) € AR: (510 –40,900) €	**New active substance and generic** 3,830 €	**New active substance and generic** (2,050 – 12,780) € AR: (510 –40,900) €	**New active substance and generic** 3,830 €
DK (IDRAC 21565)	**Invoice** The amount to be paid is invoiced to the applicant after submission. Fees to be paid within one month as indicated in the invoice **DKK**= Danish Krone	**New active substance** 265,597 DKK (35,603€) **Generic** 246,515 DKK (33,045€)	**New active substance** 168,920 DKK (22,644€) **Generic** 156,914 DKK (21,034€)	**New active substance and generics** 75,415 + 83,759 = 159,174 DKK (21,337 €)	**New active substance** 71,421DKK (9,574 €) **Generic** 71,421DKK (9,574 €)

Countries (ISO country codes)	Modality of payment	DCP RMS	DCP CMS	RMP RMS	RMP CMS
EE (IDRAC 41353**)**	**Proof of Payment** **An additional state fee of** 32 € should be paid for the application before submission and the proof of payment should be attached to the dossier.	**New active substance** 1,275 €+14,000 € **Generic (traditional herbal +homeopatic)** 958 €+14,000 €	**New active substance** 1,275 € **Generic (traditional herbal +homeopatic)** 958 €	**New active substance** 1,275 €+14,000 € **Generic (traditional herbal +homeopatic)** 958 €+14,000 €	**New active substance** 1,275 € **Generic (traditional herbal +homeopatic)** 958 €
EL	**Proof of payment,** containing company name, product concerned, detailed description of the submission, must be included in the application dossier at the time of submission	**New active substance** 40,960 € **Generic** 30,720 €	**New active substance** 20,480 € **Generic** (with BE study required) 14,336€ **Generic** (wo BE study required) 9,216 €	**New active substance** 40,960 € **Generic** 30,720 €	**New active substance** 20,480 € **Generic** (with BE study required) 14,336€ **Generic** (wo BE study required) 9,216 €
ES (IDRAC 595)	**Proof of payment** Fees are to be paid preferably electronically both from residents and non-residents. Filling of payment form model 317 is to be done by 'non resident in Spain' applicant. Justification of payment is requested for validating the application that should be submitted within 10 days. An annual fee including pharmacovigilance activities is to be paid for all products. A fee of 757.50€ is to be paid to reserve a slot for ES to act as RMS for a Decentralized or Mutual Recognition Procedure.	**New active substance** 20,734.46 € + 25% = 25,918.08 € **Generic** 8,434.22 € +25% = 10,542.78 € 25% when acting as RMS in DCP	**New active substance** 20,734.46 € **Generic** 8,434.22 €	**New active substance** 20,734.46 € + 1/3 of 20,734.46 = 27,645.95 € **Generic** 8,434.22 € + 1/3 of 8,434.22 € = 11,245.63 € One third of the amount to be paid when acting as RMS in MRP	**New active substance** 20,734.46 € **Generic** 8,434.22 €
FI (IDRAC 26004)	**Proof of payment** Fees must be paid before submission of the application and the proof of payment must be attached to the application documents An annual fee depending on the type of registered products (classic, herbal, homeopathic, parallel import) needs to be paid. This fee is for medicinal products 1,350 €.	**New active substance** 13,000 € + 12,000 € = 25,000 € **Generic** 8,000 € +12,000 € = 20,000€	**New active substance** 10,000 € **Generic** 6,000 €	**New active substance** 13,000 € + 12,000 € = 25,000 € **Generic** 8,000 € +12,000 € = 20,000€	**New active substance** 10,000 € **Generic** 6,000 €

Countries (ISO country codes)	Modality of payment	DCP RMS	DCP CMS	RMP RMS	RMP CMS
FR (IDRAC 6966**)**	**Proof of payment** A Remittance Form of Payment is to be filled in and sent together with the check or wire transfer. The payment should be made in advance of application submission so that the receipt can be attached to the application	**New active substance** 50,000 € **Generic** 14,000 € +7,000 € = 21,000€	**New active substance** 34,000 € **Generic** 14,000 €	**New active substance** 50,000 € **Generic** 14,000 € +7,000 € = 21,000€	**New active substance** 34,000 € **Generic** 14,000 €
HR (IDRAC 75145)	**Proof of payment** The payment should be made through a software application that generates a proforma invoice Proof of payment of an administrative tax (40 €) has to be attached to the submission. **HRK**= Croatian Kuna	**New active substance** 200,000 **HRK** *(26,394 €)* **Generic** 150,000 **HRK** *(19,796 €)*	**New active substance** 30,000 **HRK** *(3,959 €)* **Generic** 30,000 **HRK** *(3,959 €)*	**New active substance** 120,000 **HRK** *(15,836 €)* **Generic** 90,000 **HRK** *(11,877 €)*	**New active substance** 30,000 **HRK** *(3,959 €)* **Generic** 30,000 **HRK** *(3,959 €)*
HU (IDRAC 14226)	**Proof of payment** There are 2 different fees to be paid: one for conducting authorization procedures (to the National Institute for Quality- and Organizational Development in Healthcare and Medicines) and the other for issuing licenses (to the National Institute for Quality- and Organizational Development in Healthcare and Medicines National Institute of Pharmacy) **HUF**= Hungarian Forint	**New active substance** 3,150,000 **HUF** *(10,175 €)* **Generic** 1,575,000 **HUF** *(5,087 €)*	**New active substance** 2,250,000 **HUF** *(7,268 €)* **Generic** 1,175,000 **HUF** *(3,795 €)*	**New active substance** 3,150,000 **HUF** *(10,175 €)* **Generic** 1,575,000 **HUF** *(5,087 €)*	**New active substance** 2,250,000 **HUF** *(7,268 €)* **Generic** 1,175,000 **HUF** *(3,795 €)*
IE (IDRAC 612 and 174403)	**Proof of payment** Payment of fees to be done by check or bank transfer. A receipt of payment does not exist, although the fees should be paid by submitting the application. There is a special Fee Application Form that should be filled in and submitted with the application. In the AF are indicated prices for every application type.	**New active substance** 40,000 € **Generic** 20,000 €	**New active substance** 15,211 € **Generic** 7,658€	**New active substance** 15,211 € + 10,962 € (supplement for entire MA range)= 26,173 € +submission at the same time of an additional form (5,090 €) and/or additional strength (656€). **Generic** 7,658 € + 7,126 € =14,748 €	**New active substance** 10,647€ +submission at the same time of an additional form (3,660 €) and/or additional strength (656 €). **Generic** 5,350 €

Countries (ISO country codes)	Modality of payment	DCP RMS	DCP CMS	RMP RMS	RMP CMS
IS (IDRAC 31190)	**Invoice** Payment should be done based on the invoice issued by the Icelandic Medicine Agency. Additional details are provided within. An annual fee is to be paid for maintenance of the drug catalogues, the registration of adverse reactions and the information service in respect of medicinal products which have a marketing authorization in Iceland. **ISK**= Icelandic Krona	**New active substance** 4,000,000 **ISK** (*27,040 €)* **Generic** 2,900,000 **ISK** (*19,604 €)*	**New active substance** 300,000 **ISK** (*2,028 €)* **Generic** 260,000 **ISK** (*1,758 €)*	**New active substance** 4,000,000 **ISK** (*27,040€)* **Generic** 2,900,000 **ISK** (*19,604€)*	**New active substance** 300,000 **ISK** (*2,028 €)* **Generic** 260,000 **ISK** (*1,758 €)*
IT (IDRAC 3234)	**Proof of payment** The payments should be done online, via the new Electronic Central Collection System established between Italian Medicines Agency and Banca Popolare di Bari. The new system is available under the following address: https://www.agenziafarmaco.gov.it/Pol. Two different payments are to be accomplished, one to the Italian Ministry of Health the other to AIFA.	**New active substance** 61,248 € (10.210,04 € for AIFA+ 51.037,96 € for Ministry) **Generic** 23,760 € (3.960,79 € for AIFA+ 19.799,21 € for Ministry)	**New active substance** 61,248 € (10.210,04 € for AIFA+ 51.037,96 € for Ministry) **Generic** 23,760 € (3.960,79 € for AIFA+ 19.799,21 € for Ministry)	**New active substance** 61,248 € (10.210,04 € for AIFA+ 51.037,96 € for Ministry) **Generic** 23,760 € (3.960,79 € for AIFA+ 19.799,21 € for Ministry)	**New active substance** 61,248 € (10.210,04 € for AIFA+ 51.037,96 € for Ministry) **Generic** 23,760 € (3.960,79 € for AIFA+ 19.799,21 € for Ministry)
LT (IDRAC 42031, 206927)	**Proof of payment** The signed proof of payment for the entire fee is to be submitted with the application form to the State Medicine Control Agency. An explanation form concerning the payment details is to be filled in by the MAH and submitted	**New active substance** 11,466.93 € **Generic** 8,113.99 €	**New active substance** 626.45 € **Generic** 344.65 €	**New active substance** 6,213.22 € **Generic** 4,306.94 €	**New active substance** 626.45 € **Generic** 344.65 €
LU (IDRAC 31188)	**Proof of payment** The proof of payment is to be attached to the application dossier	**New active substance** 12,500 € **Generic** 12,500 €	**New active substance** 600 € **Generic** 600 €	**New active substance** 12,500 € **Generic** 12,500 €	**New active substance** 600 € **Generic** 600 €
LV (IDRAC 40671, 96622)	**Proof of payment** Fees are to be submitted before submitting the application dossier. A payment application form is to be filled in and submitted electronically to	**New active substance** 4,268.62 € - 14,228.72 € + 9,923.32 € per procedure	**New active substance** 4,268.62 €	**New active substance** 2,845.74 € + 5,647.30 € = 8,520.04 €	**New active substance** 2,845.74 €

Countries (ISO country codes)	Modality of payment	DCP RMS	DCP CMS	RMP RMS	RMP CMS
	rekini@zva.gov.lv. After receiving the invoice and fee payment, the copy of SAM invoice is to be attached to the dossier. There are 2 invoices issued with the same invoice number: one preliminary invoice in advance and the other after finalization of procedure.	**Generic** 4,268.62 € + 9,923.32 € = 14,191.94 €	**Generic** 4,268.62 €	**Generic** 2,845.74 € + 5,647.30 € = 8,520.04 €	**Generic** 2,845.74 €
MT (IDRAC 44263)	**Proof of payment** The proof of payment is to be submitted together with the application dossier.	**New active substance** 140,000 € **Generic** 125,000 €	**New active substance** 250 € **Generic** 250 €	**New active substance** 140,000 € **Generic** 125,000 €	**New active substance** 250 € **Generic** 250 €
NL (IDRAC 216)	**Invoice** Even if the Medical Low of Netherlands is stating that the proof of payment is to be submitted with the application, this practice is at the moment not in force and an invoice is provided after dossier submission. If the fees are not paid within 30 days after invoice receipt the assessment of the application will be suspended. A package fee is applying when more applications for different forms and strengths are submitted at the same time. When NL acts as RMS for a RMP, a surcharge is added to the package fee. An annual fee is to be paid for each registered product.	**New active substance** 63,470 € **Generic** 36,870 €	**New active substance** 31,375 € **Generic** 18,435 €	**New active substance** 63,470 € **Generic** 13,810 € + 23,060 € = 36,870 €	**New active substance** 19,780 € **Generic** 7,700 €
NO (IDRAC 154401)	**Invoice** After submission of the application the NoMA is issuing an invoice of the name of applicant indicated in the cover letter. The invoice is to be paid within 30 days. **NOK**= Norwegian Krone	**New active substance** 420, 000 NOK (*49,148 €)* **Generic** 190,000 NOK (*22,234 €)*	**New active substance** 210,000 NOK (*24,574 €)* **Generic** 160,000 NOK (*18,723 €)*	**New active substance** 150,000 NOK (*17,553 €)* **Generic** 150,000 NOK (*17,553 €)*	**New active substance** 155,000 NOK (*18,138 €)* **Generic** 110,000 NOK (*12,872 €)*
PL (IDRAC 14857)	**Proof of payment** The proof of payment (original copy of the transfer) is to be submitted with the dossier. When PL is acting as RMS in DCP the fee is 150% of the fee for national MA.	**New active substance** 131,250 PLN (*31,780 €)*	**New active substance** 87,500 PLN (*21,186 €)*	**New active substance** With AR preparation 65,625 PLN (*15,890 €)* With update of AR 43,750 PLN (*10,593 €)*	**New active substance** 87,500 PLN (*21,186 €)*

Countries (ISO country codes)	Modality of payment	DCP RMS	DCP CMS	RMP RMS	RMP CMS
	When PL is acting as RMS in MRP the fee for preparing the AR is 75% and for updating an existing AR is 50% of the national MA. For initiation of the referral procedure in MRP o DCP a fee of 30 % from the initial MA is required.	**Generic** 42,656 PLN (*10,328 €)*	**Generic** 28,438 PLN (*6,886 €)*	**Generic** 42,656 PLN (*10,328 €)*	**Generic** 28,438 PLN (*6,886 €)*
PT (IDRAC 627)	**Proof of payment** The application should be electronically pre-submitted in local portal and the fee should be validated by Infarmed. The validated proof of payment of fee is to be attached to the final submission.	**New active substance** 7, 672.50 € **Generic** 7, 672.50 €	**New active substance** 3,069 € **Generic** 3,069 €	**New active substance** 7, 672.50 € **Generic** 7, 672.50 €	**New active substance** 7, 672.50 € **Generic** 7, 672.50 €
RO	**Proof of payment** (payment form 14 days before submission) Tax and Tariff Payment Form is to be filled in (http://www.anm.ro/anmdm/en/med_formulare.html) Full application dossiers with RO as RMS are not accepted either in DCP nor in RMP	**New active substance** Not applicable **Generic** 8,050 €	**New active substance** 7,500 € **Generic** 5,200 €	**New active substance** Not applicable **Generic** 8,050 €	**New active substance** 7,500 € **Generic** 5,200 €
SE (IDRAC 2435)	**Invoice** No fees are to be paid with the application, as the fees will be invoiced to the applicant by NCA. Payment details will be indicated in the invoice. Before acting as RMS a national application must have been approved, therefore the fees for national applications are to be paid first. An extra tax is charged when SE is acting a RMS. **SEK**= Swedish Krona	**New active substance** (400,000+200,000) SEK=600,000 SEK (*64,422 €)* **Generic** (200,000+200,000) SEK=400,000 SEK (*42,948 €)*	**New active substance** 100,000 SEK (*10,737 €)* **Generic** 100,000 SEK (*10,737 €) –substances not approved in SE* 65,000 SEK (*6,979 €) – substances approved in SE*	(**New active substance** (400,000+200,000) SEK=600,000 SEK (*64,422 €)* **Generic** (200,000+200,000) SEK=400,000 SEK (*42,948 €)*	**New active substance** 100,000 SEK (*10,737 €)* **Generic** 100,000 SEK (*10,737 €) – substances not approved in SE* 65,000 SEK (*6,979 €) – substances approved in SE*
SI (IDRAC 40804, 208036)	**Invoice** Payment can be done only after the reference number of the procedure. The applicants will receive e-mail with details on information related the legal basis, the amount to be paid and the reference number. The payment should be done within 15 days after this notice. There is an annual fee to be paid for product already on the market.	**New active substance** 35,000 € **Generic** 29,000 €	**New active substance** 2,250 € **Generic** 1,900 €	**New active substance** 30,000 € **Generic** 25,000 €	**New active substance** 2,100 € **Generic** 1,800 €

Countries (ISO country codes)	Modality of payment	DCP RMS	DCP CMS	RMP RMS	RMP CMS
SK (IDRAC 14044)	**Proof of payment** The fees are to be paid via bank transfer before submission of the application. Via the electronic application of the marketing authorization the applicant will receive the variable symbol identification number that is to be used when doing the payment transfer.	**New active substance** 11,000 € **Generic** 9,000 €	**New active substance** 6,000 € **Generic** 5,000 €	**New active substance** 11,000 € **Generic** 9,000 €	**New active substance** 6,000 € **Generic** 5,000 €
UK (IDRAC 519)	**Proof of payment** Proof of payment is to be submitted with the application. When the companies are using the MHRA's iRIS online account management facility for the marketing authorizations applications the PoP would be a copy of the automated email the applicant receive from MHRA on payment receipt. Other alternative PoP are also accepted. Additional fees apply for regulatory assistance (IDRAC 45589, 122269). **GBP**= Pound Sterling	**New active substance** 143,134 GBP (*199,623 €)* **Generic** 18,422 GBP (*25,693 €)*	**New active substance** 99,507 GBP (*138,778 €)* **Generic** 10,087 GBP (*14,068 €)*	**New active substance** 103,059 GBP (*143,732 €)* **Generic** 10,447 GBP (*14,570 €)*	**New active substance** 69,357 GBP (*96,729 €)* **Generic** 7,056 GBP (*9,840 €)*

Annex VII - Fees for Renewals (for new active ingredient, first pharmaceutical form and strength). Information is obtained from IDRAC 116702 and 49677. The paying modalities are the same with those presented in **Annex VI-Fees for initial MAA**. Specific information is presented under **Comments**.

Approximated changes are given according to the official rate of 30-May -2015.

Countries (ISO country codes)	DCP RMS	DCP CMS	RMP RMS	RMP CMS	Comments (IDRAC 116702 and 49677)
AT	Included in the annual fee				
BE	2,285.30x2 =4,570.60 €	2,285.30 €	2,285.30x2 =4,570.60 €	2,285.30 €	
BG	10,000 **BGN** (5,111 €)	5,000 **BGN** (2,556 €)	8,000 **BGN** (4,089 €)	4,000 **BGN** (2,044 €)	
CY	3,410+3,410 €	512+512 €	3,410+3,410 €	512+512 €	The first fee is to be paid with the submission of the dossier, the second one with the issue of the renewal decision.
CZ	200,000 **CZK** (7,288 €)	80,000 **CZK** (2,915 €)	200,000 **CZK** (7,288 €)	80,000 **CZK** (2,915 €)	
DE (BfArM)	9,600 € (without EA)	4,000 € (without EA)	9,600 € (without EA)	4,000 € (without EA)	Reduction of fees with the new 3rd decree of March 2015 [55]; EA=Environmental Assessment
DE (PEI)	3,120 €	3,120 €	3,120 €	3,120 €	In case extensive resources and external expertise is required, the fees might be increased up to twice
DK	13,855+13,718 DKK (3,696 €)	17,811 DKK (2,386 €)	13,855+13,718 DKK (3,696 €)	17,811 DKK (2,386 €)	When DK is RMS, a fee for PSUR evaluation (13,855 DKK in DCP and 13,718 DKK in MRP) must be added beside the renewal fee**.**
EE	3,693 €	639 €	3,693 €	639 €	In addition a fee of 32 € is to be paid by issuing the renewal certificate.
EL	7,168 €	5,120 €	7,168 €	5,120 €	The fee includes all forms and strengths.
ES	2,342.71 € +25%	2,342.71 €	2,342.71 €	2,342.71 €	When during the DCP with ES

Countries (ISO country codes)	DCP RMS	DCP CMS	RMP RMS	RMP CMS	Comments (IDRAC 116702 and 49677)
	=2,928.39 €				as RMS a national renewal will be granted, the fee is increased with 25%.
FI	2,000 €	No additional fee.	2000 €	No additional fee.	The fees for FI acting as CMS are included in the annual fee.
FR	5,000 €	5,000 €	5,000 €	5,000 €	
HR	40,000 **HRK** (5,279 €)	20,000 **HRK** (2,639 €)	40,000 **HRK** (5,279 €)	20,000 **HRK** (2,639 €)	Fees valid since accession of HR in EU
HU	1,575,000 **HUF** (5,087 €)	1,125,000 **HUF** (3,634 €)	1,575,000 **HUF** (5,087 €)	1,125,000 **HUF** (3,634 €)	
IE	1,000 €	No fees	1,000 €	No fees	
IS	630,000 **ISK** (4,259 €)	130,000 **ISK** (879 €)	630,000 **ISK** (4,259 €)	130,000 **ISK** (879 €)	
IT	3,062.40 €	3,062.40 €	3,062.40 €	3,062.40 €	
LI	Not available	Not available	Not available	Not available	
LT	1,930 €	338 €	1,930 €	338 €	
LU	Not available	Not available	Not available	Not available	
LV	2,845.72 €+4,268.62 €	2,845.72 €	2,845.72 €+4,268.62 €	2,845.72 €	
MT	1,000 €	450 €	1,000 €	450 €	
NL	No fees	No fees	No fees	No fees	
NO	45,000 **NOK** (5,266 €)	45,000 **NOK** (5,266 €)	45,000 **NOK** (5,266 €)	45,000 **NOK** (5,266 €)	
PL	14,219 **PLN** (3,443 €)	10,938 **PLN** (2,648 €)	14,219 **PLN** (3,443 €)	10,938 **PLN** (2,648 €)	
PT	2,404.05 €	1,759.56 €	2,404.05 €	1,759.56 €	
RO	4,305 €	2,100 €	4,305 €	2,100 €	
SE	Included in the annual fee (since 01-Jan 2011)				

Countries (ISO country codes)	DCP RMS	DCP CMS	RMP RMS	RMP CMS	Comments (IDRAC 116702 and 49677)
SI	11,750 €	1,250 €	11,750 €	1,250 €	
SK	5,000 €	4,000 €	5,000 €	4,000 €	
UK	10,758 **GBP** (15,004 €)	None	10,758 **GBP** (15,004 €)	None	

Annex VIII - Fees for MRP Variations (for new active ingredient, first pharmaceutical form and strength). Information is obtained from IDRAC 45593. The paying modalities are the same with those presented in Annex VI. Specific information is presented under **Comments**.

Approximated changes are given according to the official rate of 30-May-2015.

Countries (ISO country codes)	Type IA Variation		Type IB Variation		Type II Variation		Extension		Comments (IDRAC 45593)
	RMS	CMS	RMS	CMS	RMS	CMS	RMS	CMS	
AT	Included in the annual fee								
BE	914.10 €	475.05 €	1,523.54 €	761.77 €	1,523.54 € to 6,094.14 €	761.77 € to 3,047.07 €	See comment	See comments	The fees for extension application are the same as for original dossier application. Fees for MRP=fees for DCP
BG	1,500 **BGN** (767 €)	1,000 **BGN** (511 €)	1,500 **BGN** (767 €)	1,000 **BGN** (511 €)	2,000 **BGN** (1,022 €)	1,500 **BGN** (767 €)	8,000 **BGN** (4,089 €)	8,000 **BGN** (4,089 €)	The fees for extension application are the same as for original dossier application
CY	341 €	85 €	341 €	85 €	3,410 €	341 €	8,540+8,540 €	512+512 €	In case of extensions, the 1st fee is to be paid by submission, the second by issuing the MA.
CZ	12,000 **CZK** (437 €)	4,000 **CZK** (146 €)	25,000 **CZK** (911 €)	10,000 **CZK** (364 €)	100,000 **CZK** (3,644 €) or 120,000 **CZK** (4,373 €) (see comments)	50,000 **CZK** (1,822 €) or 70,000 **CZK** (2,551 €) (see comments)	100,000 **CZK** (3,644 €)	40,000 **CZK** (1,458 €)	An administrative fee of 2,000 **CZK** (73 €) is to be paid for each application. If the type II VAR is including a new bioequivalence study the fee is increase with 20,000 **CZK**
DE (BfArM)	370 €	190 €	1,800 € (without EA)	400 € (without EA)	4,300 € to 15,600 €	1,700 € to 7,800 €	4,800 € to 9,700 € in addition to the basic MA fee	3,400 € to 5,700 € in addition to the basic MA fee	Reduction of fees with the new 3rd decree of March 2015 [64].

Countries (ISO country codes)	Type IA Variation		Type IB Variation		Type II Variation		Extension		Comments (IDRAC 45593)
	RMS	CMS	RMS	CMS	RMS	CMS	RMS	CMS	
DE (PEI)	660 €	430 €	1,250 €	800 €	550 € to 40,900 €	500 € to 40,900 €	2,050 € to 12,780 € AR: 510 € to 20,450 €	1,915 €	PEI is charging a fee for acting as RMS in MRP procedure plus the fee for Assessment Report (AR) Fees for MRP=fees for DCP
DK	2,076 DKK (278 €)	1,327 DKK (178 €)	2,076 DKK (278 €)	1,327 DKK (178 €)	8,300 to 13,855 DKK (1,113 € to 1,857 €)	1,795 DKK (241 €)	34,705 DKK (4,652 €)	16,367 to 17,811 DKK (2,194 € to 2,388 €)	When DK is acting as RMS in MRP or DCP, to the fees of the VAR type IA, IB and II is added a national variation fee (corresponding to the same fee type)
EE	No Fee	No Fee	100 € + 500 €	500 €	383 € +1,000 €	383 €	511 € + 14,000 € (for all strength of the pharmaceutical forms submitted together)	511 €	A state fee of 16 € (type I and II VARs) or 32 € (extensions) is to be paid in addition.
EL	1,024 €	512 €	2,048 €	1,024 €	3,072 € to 10,240 €	2,048 € to 5,120 €	10,240 €	10,240 €	
ES	727.42 € +25% = 909.28 €	727.42 €	1,249.22 € +25% =1,561.53 €	1,249.22 €	7,122.25 € +25% =8,902.81 €	7,122.25 €	70% of the first product authorization +25%	70% of the first product authorisation	The fees of the variations are raised with 25% when ES is acting as RMS
FI	500 €	No fee	1,500 €	400 €	3,000 € (6,000 € for a new therapeutic indication)	800 € (see also comments)	18,000 €	6,000 €	For Type II VARs when FI is CMS the change in the PSUR periodicity is free of charge and the basis fee for a new therapeutic indication is 3,000 €:

Countries (ISO country codes)	Type IA Variation		Type IB Variation		Type II Variation		Extension		Comments (IDRAC 45593)
	RMS	CMS	RMS	CMS	RMS	CMS	RMS	CMS	
FR	1,400 €	1,400 €	1,400 €	1,400 €	1,400 € to 22,000 €	1,400 € to 22,000 €	14,000 € to 23,000 €	14,000 € to 23,000 €	22,000 € for Type II VAR regarding a new indication and 23,000 € for extension with new indication
HR	5,000 **HRK** (660 €)	2,500 **HRK** (330 €)	7,000 **HRK** (924 €)	3,500 **HRK** (462 €)	9,000 **HRK** to 20,000 **HRK** (1,188 € to 2,639 €)	3,500 **HRK** to 10,000 **HRK** (462 € to 1,320 €)	500 **HRK** (66 €)	500 **HRK** (66 €)	
HU	250,000 **HUF** (808 €)	180,000 **HUF** (581 €)	250,000 **HUF** (808 €)	180,000 **HUF** (581 €)	350,000 **HUF** (1,131 €)	270,000 **HUF** (872 €)	Same fee as for original dossier	Same fee as for original dossier	
IE	No fee (see comment)	No fee (see comment)	338 €	345 € +468 €	506 € + 338 € to 2,601 € + 525 €	338 € to 1,797€	7,658 € + 2,859 €	5,350 €	For VAR type IA no fees are required except for category C.I.3a -100 €
IS	49,000 **ISK** (331 €)	12,000 **ISK** (81 €)	77,000 **ISK** (520 €)	25,000 **ISK** (169 €)	300,000 **ISK** to 630,000 **ISK** (2,028 € to 4,259 €)	40,000 **ISK** to 50,000 **ISK** (270 € to 338 €)	1,260,000 **ISK** (8,518 €)	100,000 **ISK** (676 €)	
IT	660 €	660 €	1,531.20 €	1,531.20 €	18,374.40 €	18,374.40 €	18,374.40 €	18,374.40 €	Fees might be reduced to 5,326.40 € or 9,178.20 € for some type II VARs
LT	181.88 €	66.32 €	317.71 €	164.50 €	1,195.26 € to 1,598.12 €	405.18 € to 576.63 €	2,453.08 €	318 €	
LU	No fee	No fee	No fee	No fee	No fee	No fee	No fee	No fee	
LV	142.29 € + 426.86 €	142.29 €	142.29 € + 426.86 €	142.29 €	142.29 € to 426.86 € + 853.72 €	142.29 € to 426.86 €	2,845.74 € + 7,114.36 € per procedure	2,845.74 €	70% discount for additional registration numbers (if VAR is included in one application form and submitted as one variation within a group of variations)
MT	115 €	No fee	350 €	No fee	800 € to 4,000€	No fee	10,000 €	250 €	

Countries (ISO country codes)	Type IA Variation		Type IB Variation		Type II Variation		Extension		Comments (IDRAC 45593)
	RMS	**CMS**	**RMS**	**CMS**	**RMS**	**CMS**	**RMS**	**CMS**	
NL	Included in the annual fee	Included in the annual fee	Included in the annual fee	Included in the annual fee	Included in the annual fee	Included in the annual fee	28,790€	3,660 €	Line extensions are package fees that cover all simultaneously applications by a single applicant for different form and strengths
NO	No fee	No fee	No fee except variations leading to changes in product information	No fee except variations leading to changes in product information	90,000 **NOK** (10,532 €)	45,000 **NOK** (5,266 €)	125,000 **NOK** (14,628 €)	110,000 **NOK** (12,872 €)	Worksharing fees exist: Type IB and other Type II: 13,000 NOK (1,521 €); **NO is RMS**: Indication, dosing:90,000 NOK (10,532 €) **NO is CMS**: Indication, dosing:45,000 NOK (5,266 €). One fee is to be paid for VAR including several forms /strengths and for VARs that leads to more consequential VARs.
PL	6,563 **PLN** (1,589 €)	4,375 **PLN** (1,059€)	6,563 **PLN** (1,589 €)	4,375 **PLN** (1,059 €)	26,250 **PLN** (6,356 €)	17,500 **PLN** (4,237 €)	See comments	See comments	Fees are calculated as a percentage of the basic value of 1,750 **PLN** (424 €) and vary considerably depending on the type of product. For extension application same fee applies as for original dossier.

Countries (ISO country codes)	Type IA Variation		Type IB Variation		Type II Variation		Extension		Comments (IDRAC 45593)
	RMS	**CMS**	**RMS**	**CMS**	**RMS**	**CMS**	**RMS**	**CMS**	
PT	797.94 €	797.94 €	797.94 €	797.94 €	1,585.65 €	1,585.65 €	3,166.19 €	3,166.19 €	Fees for additional strength or pharmaceutical form : for Type IA and IB are 271.10 € and for Type II are 511.50 € and for
RO	460 €	300 €	760 €	500 €	2,400 €	1,600 €	Not available	Not available	
SE	Included in the annual fee				20,000 **SEK** (2,147 €)	6,000 **SEK** (644 €)	200,000 **SEK** +200,000 **SEK** (42,948 €)	65,000 **SEK** (6,979 €)	The extension fee when SE is RMS is for all strengths and pharmaceutical forms of same product submitted at the same time
SI	2,000 €	250 €	4,000 €	550 €	6,500 €	700 €	15,000 €	1,250 €	
SK	200 €	200 €	200 €	200 €	5,000 €	3,200 €	2,000 €	2,000 €	
UK	No fee	No fee	611 **GBP** (852 €)	308 **GBP** (430 €)	989 **GBP** to 28,492 **GBP** (1,379 € to 39,737 €)	816 **GBP** to 39,829 **GBP** (1,138 € to 55,548 €)	28,492 **GBP** (39,737 €)	19,256 **GBP** (26,856 €)	

Annex IX – Submission modalities (according to CMDh guidelines [31], [37] and CESP Contacts [66]. In case of issues with the CESP submission, NCAs may request CD/DVD.

Countries (ISO country codes)	CESP Submission accepted (Yes/No); national portals	Submission on CD/DVD and/or paper documents	Comment
AT	**YES**	1 x CD/DVD .	If DVDs/CDs and/or PAPER documents are sent in parallel with the dossier through CESP, these should be marked with the relevant CESP-submission number. (CESP Contacts)
BE	**YES**	1 x CD/DVD +copy of CL	No parallel submission on CD, DVD or eudralink is allowed (CESP Contacts)
BG	**NO**	2x CD/DVD + signed CL + signed AF	For notifications art 61 (3) and all VAR types only 1 CD/DVD is enough
CY	**YES**	1X CD/DVD + signed CL+ signed AF	Originally signed application form and cover letter in hard copy must be provided with each CESP submission (CESP Contacts)
CZ	**YES** (except ASMF and PSUR)	1X CD/DVD + signed CL + signed AF	Powers of attorney with the original signature should be sent by post or courier, so that the original power of attorney is ideally delivered on the same day as the submission via CESP or close to this date. (CESP Contacts)
DE	**YES;** submission of VARs through the national portal PharmNet.Bund is highly recommended.	(1X) CD/DVD + CL	Draft response documents submitted for pre-assessment when DE is acting as RMS are not accepted via CESP. (http://www.bfarm.de/EN/Drugs/licensing/ZulRelThemen/eSubmission/cesp.html?nn=360139)
DK	**YES** (except Clinical Trials)	1 CD/DVD + signed CL	
EE	**YES**	1X CD/DVD	
EL	**NO**	3X CD/DVD for M 1 to 3 (M 4 and 5 only in electronic format)+ signed AF in Greek language	According to http://www.eof.gr/web /guest /procedures For REN and VAR a paper version of module 1 is required with the CD/DVD [61] Difference between the info in the new CMDh guidelines [31, 37] and the CESP Contact website.
ES	**YES** (except lifting of a suspension, withdrawal, national procedures and PSUR); national portal RAEFAR must be used https://sede.aemps.gob.es /en/home.htm	1X CD/DVD +signed CL + signed AF	In case the size of the documentation for the National Procedure is greater than 50 MB, documentation to be sent via CESP (CESP Contacts). According to ***IDRAC 5211*** submission of REN through CESP is not possible. This information is not posted on the CESP website.
FI	**YES** (except ASMF/DMF, DSUR, clinical trials);	2X CD/DVD +signed CL + signed AF	PSUR and RMP submissions are accepted if submitted as eCTD sequences (CESP Contacts)
FR	**YES** (but still in a pilot phase)	1 x CD/DVD + signed CL + signed AF	For CESP submission in the pilot phase only one activity per submission is accepted, in eCTD and NeeS format.(CESP Contacts)
HR	**YES**	1 x CD/DVD + signed CL + signed AF	In parallel to the electronic dossier submission, a Cover letter, an Application form and Letters of authorisation must be submitted in original paper

Countries (ISO country codes)	CESP Submission accepted (Yes/No); national portals	Submission on CD/DVD and/or paper documents	Comment
			copies with wet signature(s).
HU	**NO**	1 x CD/DVD + signed CL + signed AF	
IE	**YES**	1X CD/DVD + copy of CL	
IS	**YES**	1X CD/DVD + copy of CL	
IT	**YES** (in testing phase and CESP submission considered only supportive). For VAR application submission through the national portal (Portali Variazione) is strongly recommended.	1 x CD/DVD + signed CL + signed AF	For MAA, VAR applications, MAH transfers and any responses to these applications submitted through MR/DC procedures, ASMF deposits or ASMF amendments only submission through standard channels is considered official submission. These applications should be submitted in paper accompanied by complete documentation on CD/DVD. For VAR application submission through the national portal (Portali Variazione) is strongly recommended (CESP contacts), but in parallel with the submission in paper and on CD. (Portali Variazione)
LT	**YES**	1 x CD/DVD + signed CL + signed AF	Even if submission through CESP is allowed sending of originally signed documents Application Form, Cover Letter, Proof of Payment and Power of Attornay is required (CESP Contacts)
LU	**YES**	1 x CD/DVD + copy of CL (initial MAA) +signed CL (VARs+REN)	In addition to CESP submission the filled in “Demande d’autorisation de mise sur le marché d’un medicament” and the Cover letter with the CESP number should be provided. (CESP Contacts).
LV	**YES**	1 x CD/DVD + signed CL + signed AF	Submission of documents through CESP is not mandatory; other submission ways might be choosen: CD/DVD or Eudralink, but duplication is not allowed. When submission through CESP following documents are to be submitted separately: • signed CL with CESP number; • signed AF for initial MAA, VAR or REN; • PoA if not submitted earlier; • copy of SAM invoice and a payment confirmation For submission of additional documentation only signed CL is required. (CESP Contacts)
MT	**YES**	1 x CD/DVD + copy of CL	Applications and documents should only be sent through one medium of submission (CESP, paper,CD/DVD, email or Eudralink packages), which should be stated in the CL (http://www.medicinesauthority.gov.mt /requirementssubmission.)
NL	**YES**	1 x CD/DVD + signed CL + signed AF	
NO	**YES**	1 (2) X CD/DVD +copy of CL;	When Norway is acting as RMS in a new application 2 CD/DVD are required [31].
PL	**YES**, but only initial MAA in MR/DC procedures are allowed. The CESP submission is still in the pilot phase.	1 x CD/DVD + signed CL, AF and other originally documents	In case of CESP submission, all documents, previously needed originally hand signed, can be acknowledged with certified electronic signature. Paper documentation, as well as CD/DVD submissions are allowed, but these should not be mixed up with CESP submission.

Countries (ISO country codes)	CESP Submission accepted (Yes/No); national portals	Submission on CD/DVD and/or paper documents	Comment
PT	**YES** (except ASMF and PMF) **MAA**: CESP submission only after completion of pre-submission in the INFARMED portal http://www.infarmed.pt /pt/medicamentos /uso_humano/redirect.html VAR: Submission should be done via the national portal: http://www.infarmed.pt /pt/medicamentos/ uso_humano/submissao_alter acoes /index.html. Only in case of submissions exceeding 10 MB these should be done in parallel through CESP and national portal	4 x CD/DVD (for MAAs) or 1X CD/DVD (for VARs and REN) + signed CL + signed AF	CESP submissions of a new application should be done after pre-submission in the national portal and confirmation of valid payment of fee. INFARMED requires originally signed cover letter, originally signed application form and proof of payment. (CESP contacts)
RO	**YES** (except Clinical Trial Submission);	1 x CD/DVD + signed CL + signed AF	CESP for biological products in the test phase.
SE	**YES**	1 x CD/DVD +copy of CL	Only one way of submission should be used (CESP, email/EudraLink or CD/DVD)
SI	**YES**	1 x CD/DVD + signed CL	Specific Slovenian Cover letter and application Form must either be signed by an advanced electronic or originally hand-signed and sent in parallel with the CESP submission in physical form.
SK	**NO**	1 x CD/DVD + signed CL + signed AF	
UK	**YES** Submission through MHRA portal https://www.gov.uk/mhra-portal-register-to-submit-forms is recommended.	1 x CD/DVD +copy of CL	According to IDRAC 39066 submission through MHRA portal is required.

Annex X – Timelines for granting national marketing authorizations and national approvals for Type II variations

Country	Timelines for granting national marketing authorization	Timelines for approval of type II variations after positive opinion by RMS
Austria (AT):	2-3 months	~ 2 months.
Belgium (BE)	1-2 months	30 days
Bulgaria (BG)	4-6 months	n.a.
Croatia (HR)	1-2 months	30 days
Cyprus (CY)	5-7 months	not specific timeline
Czech Republic (CZ)	1-2 months	~ 2 months
Denmark (DK)	1-2 months	~ 3 months
Estonia (EE)	1-2 months	~ 2 months
Finland (FI)	2-3 months	~ 2 months
France (FR)	3-4 months	3-4 months
Germany (DE)	1-2 months	~ 2 months
Greece (EL)	5-7 months	3-5 months
Hungary (HU)	1-2 months	~ 2 months
Iceland (IS)	1-2 months	~ 12 months
Ireland (IE)	1-2 months	4- 6 months
Italy (IT)	3-4 months	6-9 months
Latvia (LV)	2-3 months	3 months
Lithuania (LT)	within 1 month	4-6 months
Luxembourg (LU)	3-4 months	After receiving BE or DE approvals
Malta (MT)	1-2 months	n.a
Netherlands (NL)	within 1 month	2-3 months

Country	Timelines for granting national marketing authorization	Timelines for approval of type II variations after positive opinion by RMS
Norway (NO)	1-2 months	1-3 months
Poland (PL)	3-4 months	7-9 months
Portugal (PT)	1-2 months	1 month
Romania (RO)	4-6 months	~ 12 months
Slovakia (SK)	3-4 months	~ 2-3 months
Slovenia (SI)	2-3 months	~ 2-3 months
Spain (ES)	2-3 months	~6-8 months
Sweden (SE)	1-2 months	~ 1-3 months
United Kingdom (UK)	within 1 month	1-2 months

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