Describe the CADREAC-procedure for a product which was authorized via mutual recognition procedure in the EU and compare the CADREAC-procedure with the national procedure in one CADREAC country (e.g. Romania)

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LIST OF ABBREVIATIONS

AR	Assessment Report
Art	Article
ATC	Anatomical Therapeutic Chemical
CA	Competent Authority
CADREAC	Collaboration Agreement of Drug Regulatory Authorities in European Union Associated Countries
C-CMS	CADREAC Concerned Member State
CCP	Common CADREAC Procedure
CEEC	Central and Eastern European Country
CHMP	The Committee for Medicinal Products for Human Use
CMS	Concerned Member State
CP	Centralized Procedure
CPMP	The Committee for Proprietary Medicinal Products (now named: CHMP)
CPP	Certificate of a Pharmaceutical Product
CTD	Common Technical Document
DP	Decentralized Procedure
DRA	Drug Regulatory Authority
EC	European Commission
EEC	European Economic Community
EDMF	European Drug Master File
EMEA	European Medicines Agency (formerly: The European Agency for the Evaluation of Medicinal Products)
EPAR	European Public Assessment Report

EU	European Union
GMP	Good Manufacturing Practice
INN	International Non Proprietary Name
MA	Marketing Authorization
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MRFG	Mutual Recognition Facilitation Group
MRP	Mutual Recognition Procedure
MS	Member State
MP	Medicinal Product
NMA	National Medicines Agency
NP	National Procedure
NtA	Notice to Applicants
PIL	Patient Information Leaflet
PSUR	Periodic Safety Update Report
REN	Renewal
RMS	Reference Member State
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
VAR	Variation
WHO	World Health Organization

I. INTRODUCTION

The **C**ollaboration **A**greement of **D**rug **R**egulatory Authorities in **E**uropean **U**nion **A**ssociated **C**ountries (CADREAC) was a collaboration of 12 countries, which started in 1997. The Heads of Drug Regulatory Authorities (DRAs) in the European Union (EU) associated countries agreed to sign the CADREAC agreement in order to start a formal collaboration during the first meeting of DRAs in Central and Eastern Europe Countries (CEECs), 12 to 14 June 1997 in Sofia.

Up to April 2005, 12 state regulatory authorities for human medicinal products (MPs) of countries in Central, Eastern and Southern Europe had signed the CADREAC agreement:

- Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia (since 1997)
- Slovenia (since 1998)
- Cyprus (since 1999)
- Turkey (since 2001)

As stated above, originally the members of CADREAC were Bulgaria, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, Slovenia and Turkey. Nine of these countries joined the EU at 1st May 2004, therefore in April 2005 there were only three CADREAC countries left – Bulgaria, Romania and Turkey.

The mission of CADREAC is facilitation of smooth transition of regulatory conditions in EU associated countries to achieve regulatory standards required by Acquis Communautaire (compliance to article (Art.) 6 of Directive 2001/83/EEC (cf. 7.1) amended by Directive 2004/27 (cf. 7.2): *"No MP may be placed on the market of a Member State (MS) unless a marketing authorization (MA) has been issued by the competent authorities (CAs) of that MS in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 2309/93. The authorization referred to in paragraph 1 shall also be required for radionuclide generators, radionuclide kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals."),* which are:

- Implementation of EU regulatory standards
- Involvement in professional activities within EU
- Introduction of mutually recognition procedures (MRP)
- Introduction of centralized procedures (CP)
- Development of common strategies
- Preparation of meetings
- Information exchange

A CADREAC Standard Operating Procedure (SOP), CADREAC SOP-3 (2001) was adopted in April 2001, defining the responsibilities and function of a CADREAC secretariat (cf. 7.3).
The DRA, which will act as CADREAC secretariat, is selected at CADREAC annual assembly at least one year before the term of service.
The activities of the CADREAC secretariat start with the organization of CADREAC annual meeting, including drafting of the agenda and minutes of CADREAC annual meeting. The activities end with drafting and presenting CADREAC annual report to be approved at CADREAC annual meeting and with providing all necessary information to its successor.
If no other delegation is made, CADREAC secretariat is the principle contact point for CADREAC.
The CADREAC secretariat is also responsible for:

- Maintenance of CADREAC documents, especially keeping lists updated of
  - ➔ CADREAC agreed documents (like Common procedures, SOPs, positions) except Collaboration Agreement
  - ➔ DRAs – CADREAC members and observers to CADREAC
  - ➔ CADREAC observers at European Community/European Medicines Agency (EMEA) working parties and committees
  - ➔ CADREAC experts serving as contact points for sending materials from Working Parties
- Co-ordination of distribution of relevant information, esp. drafts and final versions of CADREAC documents and co-ordination of activities needed to obtain common CADREAC opinion
- Prepare documents to be published on the CADREAC homepage

The secretariat of CADREAC is located in Romania since March 2004.

In addition to the CADREAC MSs, the following countries have the status of observers: Belarus, Bosnia-Herzegovina, Croatia, Republic of Moldova, Switzerland and Serbia and Montenegro.

The CADREAC countries developed certain guidelines and procedures as a preparation for their EU-accession.
A number of procedures and agreed documents have been published in the world wide web (on the CADREAC homepage):

- Common procedure on the granting of MAs by CADREAC DRAs for MPs authorized in the EU by CP - in force since January 1999 (cf. 7.4)
- Common procedure on the granting of MAs by CADREAC DRAs for MPs authorized in the EU by MRP - in force since May 2001 (The 1st revision of the guideline - published June 10th, 2001 - includes the retrospective inclusion of MPs for human use authorized in EU via MRP in the Common CADREAC Simplified System) (cf. 7.9)
- Common CADREAC Procedure (CCP) for retrospective inclusion of centrally authorized MPs for human use in the Common CADREAC Simplified System - in force since May 2001 (cf. 7.6)
- SOPs
- Lists of contact points
- Lists of CADREAC observers in European Community/EMEA working parties and of observers to CADREAC

The CADREAC procedures relating to regulatory activities for products authorized in EU via CP is operational since January 1st, 1999 and is described in the document *"Procedure on the granting of MAs by CADREAC DRAs for MPs for human use authorized in the EU following the CP and the variation (VAR) and renewal (REN) of such MAs"* (cf. 7.4).
The document describes the simplified CADREAC procedure as to the granting of MAs by CADREAC DRAs for centrally authorized MPs for human use and the post-authorization activities – VARs, RENs and handling of pharmacovigilance information - of such MAs.
Reference is made to the document *"Guidance for simplified procedure for MA of MPs authorized in the EU following the CP and for VARs and RENs to these MAs in CADREAC area"* (cf. 7.5 (Annex 1 of cf. 7.4)).
This simplified CADREAC procedure for products authorized in EU via CP described in this document is optional and can only be initiated at the EU marketing authorization holder's (MAH) request. This means that there is no legal obligation to use the simplified CADREAC procedure.
The simplified CADREAC procedure has entered into force on 1st January 1999.

The procedure itself consists of the following four steps (cf. 7.4):

1. *"**Initiation of the procedure***

The procedure is initiated by the EU MAH. The EU MAH notifies the EMEA (see Annex 2 cf. 7.4) that an application will be submitted in one or more countries of CADREAC DRAs and indicates:

- *The country(ies) of the CADREAC DRA concerned*
- *The name of the product in the EU, pharmaceutical form(s), strength(s) authorized in the EU*
- *International Non Proprietary Name (INN) or common name of the active substance(s)*
- *The Community MA number(s)*
- *The EU MAH*
- *The proposed MAH(s) in the country(ies) of the CADREAC DRA concerned*
- *The proposed name(s) of the product in the country(ies) of the CADREAC DRA concerned*

Furthermore, the EU MAH declares that the EMEA and the European Commission (EC) may make available to the CADREAC DRA concerned any information in relation to the quality, safety and efficacy of the above MP, using the form attached as Annex 3.

The EMEA subsequently includes this information in the relevant database.

2. Submission of the application

The applicant (i.e. proposed CADREAC MAH) submits the application in the CADREAC DRA concerned; guidance for timing of submissions in individual countries is provided in the table attached to the Annex 1. The addresses of the CADREAC DRAs are provided in Annex 4. Furthermore, the proposed CADREAC MAH certifies that the application is identical with the application accepted in the EU with the exception of the following parameters, where relevant:

- *MAH*
- *Not all package sizes authorized in the EU must be authorized in countries of CADREAC DRA; moreover also*
- *Different package sizes from those that were authorized in the EU can be applied for, if the therapeutic value is not influenced (i.e. no impact on dosage schemes and therapy), and if the change concerns different number of intact units of immediate packaging only (i.e. no impact on stability of the product)*
- *The name of the MP (in substantiated cases)*

- *As an exceptional deviation from EU conditions in the countries specified in the table of specific detailed requirements attached to Annex 1, manufacturer releasing batches or repackaging product for the country of CADREAC DRA concerned, provided that acceptable Good Manufacturing Practice (GMP) conditions are evidenced (i.e. either manufacturer approved within the Community MA or manufacturer whose GMP conditions are acceptable for the CADREAC DRA concerned)*

As different strengths and dosage forms should be submitted as separate applications and as submission of each application is optional for the applicant, different strengths and dosage forms are not mentioned among parameters defined above. The documents that should accompany such application are stated in Annex 1. The important prerequisite for this procedure is the commitment of the proposed CADREAC MAH to preserve the harmonization of the product also in the post authorisation phase. The specific dossier requirements for each CADREAC DRA (e.g. number of copies, language of dossier, submission of samples, electronic submission, fee requirements) are described in the table attached to Annex 1.

3. Outcome of the procedure

The CADREAC DRA concerned informs the EMEA (attention of Pharm. N. Wathion), with copy to the applicant, at the end of the procedure on its outcome using the form provided in Annex 5.

In case of a favorable outcome (i.e. recognition of the Commission Decision granting the EU MA) the following information will be provided:

- *Identification of the product in the EU (name, MAH, Community MA No., INN or common name of the active ingredient/s)*
- *Name of the MP in the country of CADREAC DRA concerned*
- *National MA Number(s)*
- *Name of the MAH in the country of CADREAC DRA concerned*
- *Date of issue of national MA*
- *Authorized pharmaceutical form(s), strength(s), pack size(s) (stressing missing or additional package sizes in comparison with the EU)*
- *Any differences between Summary of product characteristics (SmPC), patient information leaflet (PIL), and labelling approved by CADREAC DRA concerned and in the EU, where relevant*

- *Manufacturer releasing batches or repackaging product for the country of CADREAC DRA concerned, if different from the EU (see note in paragraph 2, third indent)*

In case of disagreement with the Commission Decision granting the EU MA, the scientific conclusions, which led to such disagreement, are provided using the same form. The CADREAC DRA concerned will also inform the other CADREAC DRAs in case of any disagreement with or modification of the Commission Decision.

4. Follow-up to the procedure

Upon receipt of information regarding the outcome of the procedure, the EMEA will include such information in the relevant database.

The EMEA will keep its scientific committee, the Committee for Proprietary Medicinal Products (CPMP) (now named: Committee for Medicinal Products for Human Use (CHMP)) informed about the finalization of any procedure initiated in accordance with the above described framework. Where necessary, the EMEA will inform the CADREAC DRA concerned of the CHMP's consideration of the issue (especially in case of disagreement with the Commission Decision)."

Annex 1 of this document, the "*Guidance for simplified procedure for MA of MPs authorized in the EU following the CP and for VARs and RENs to these MAs in CADREAC area"* (cf. 7.5) has the objective to describe the arrangements between the CADREAC DRAs, the EMEA and the EC as to the granting of MAs by CADREAC DRAs for centrally authorized MPs for human use and the post-authorization activities – VARs, RENs and handling of pharmacovigilance information - of such MAs. The document provides "*guidance for MA of MPs in CADREAC area, which have been authorized throughout the EU according to Council Regulation 2309/93 (CP) (cf. 7.7) (replaced through Council Regulation 726/2004 (cf. 7.8)) and for VARs and RENs to these MAs. The document describes the principles on which the procedure is based, proposes a procedure to be followed, documentation to be submitted and outlines the responsibilities of the parties concerned. This guidance relates to MPs MAs of which were granted by the EC on the basis of the scientific expertise of the CHMP (the scientific body of the EMEA responsible for giving a scientific opinion on medicinal products processed via the CP) and the recognition of this expertise by CADREAC DRAs."*

The guidance which describes the CADREAC procedure for products authorized in EU via MRP (simplified CADREAC MRP) is called *"Procedure on the granting of MAs by CADREAC DRAs for human MPs already authorized in EU MSs following the decentralized procedure (DP)"* (cf. 7.9, cf. 7.10). In this context, DP means the MRP in EU.
The aim of this guidance which describes the CADREAC procedure for products authorized in EU via MRP (simplified CADREAC MRP) is the description of a procedure which can be used by each CADREAC DRA for granting a MA of a MP which has been authorized in the EU MSs following the MRP including subsequent VARs and RENs.
The assessment of the Reference Member State (RMS) can be assumed to be relevant for CADREAC area because it can be expected that differences in medical practice between the EU MSs and CADREAC area are generally not of major importance for public health.
The simplified CADREAC procedure offers the possibility of harmonization of SmPC, PIL and documentation of MPs authorized in the EU MSs following the MRP with the CADREAC MSs.
It should be also considered that harmonization of innovative products authorized by CADREAC DRAs with those authorized in the EU is one of the conditions for harmonization of their generics in the future (cf. 7.9, cf. 7.10).
The simplified CADREAC procedure for products authorized in EU via MRP has entered into force on 3rd May 2001.

In the two mentioned documents describing the CADREAC procedure for products authorized in EU via CP or MRP (cf. 7.4, cf. 7.9, 7.10) the legal background, requirements and timelines for the CADREAC procedures are described.
It is important to know that for Turkey only the CADREAC procedure for products authorized in EU via CP is possible because Turkey did not join the CADREAC procedure for products authorized in EU via MRP. For the other CADREAC countries both procedures are possible.
In addition to these procedures, national procedures (NPs) still exist in the three remaining CADREAC MSs – Bulgaria, Romania and Turkey.

In the following, the legal basis, requirements and timelines of the CADREAC procedure for products authorized in EU via MRP (cf. 7.9, cf. 7.10) and the NP for new marketing authorization applications (MAAs) (cf. 7.11) will be explained and evaluated in detail on the example of Romania.

The document *"Procedure on the granting of MAs by CADREAC DRAs for human MPs, already authorized in EU MSs following the DP"* (cf. 7.9) describing the CADREAC procedure for products authorized in EU via MRP, is also implemented in the Romanian national legislation as *"Decision No. 8/04.05.2001 regarding the approval of procedure on the granting of MAs by CADREAC CAs for MPs for human use, already authorized in EU MSs following the DP"* (cf. 7.10). The content of both documents concerning the CADREAC procedure is identical.

Afterwards a comparison between both procedures – the CADREAC procedure for a MP authorized in EU via MRP and the NP - will be made to evaluate which procedure to be used for which product leading to a recommendation as referred to in the conclusion.

First of all, the legal basis and the requirement for the CADREAC procedure for products authorized in EU via MRP for new MAs will be explained. According to the legislation for the CADREAC countries, there exist two different CADREAC procedures (CADREAC procedure for products authorized in EU via CP and CADREAC procedure for products authorized in EU via MRP) depending on the procedure, which was used to get the MA in EU as explained before. The principles of these two different CADREAC procedures are the same but according to the different procedures, which were used to get the MA in EU, there are also certain differences. As the focus of this master thesis is the CADREAC procedure for products, which were authorized in EU via MRP, the CADREAC procedure for products, which were authorized via CP, will not be explained more detailed than already done in the introduction. Sections concerning post-authorization activities (VARs, RENs and handling of pharmacovigilance information) of the CADREAC procedures as well as other procedures like retrospective inclusion of MPs for human use authorized in EU via CP and MRP in the common CADREAC simplified system will also not be described in detail here.

Secondly, the legal text for the NP in Romania will be discussed with regard to the legal background, the requirements and timelines for getting a MA in Romania via NP.

Afterwards, a comparison between the CADREAC procedure and the NP will be made to evaluate which procedure to be used for which product.

In the conclusion a recommendation, based on the outcome of the comparison between the CADREAC procedure and the NP, will be given for an easier decision which procedure for which product to be used will be best.

As an outlook, the future of the CADREAC procedure especially with regard to the EU accession of Bulgaria and Romania in 2007 and the new EU legislation (changes in CP and

the differentiation between MRP and DP) and the influences on the CADREAC procedures will be discussed.

Finally a short summary of the master thesis will be given.

II. CADREAC PROCEDURE FOR A PRODUCT ALREADY AUTHORIZED IN THE EU MEMBER STATES FOLLOWING THE MUTUAL RECOGNITION PROCEDURE

2.1 General overview

As mentioned before, the legal background for the CADREAC procedure for a product, which was already authorized in EU via MRP, lies down in the document *"Procedure on the granting of MAs by CADREAC DRAs for human MPs already authorized in EU MSs following the DP"* (cf. 7.9). In this context, DP means the MRP in EU.

The purpose of this document (cf. 7.9) and the respective Romanian legislation (cf. 7.10) is to describe the simplified CADREAC procedure, which can be used by any CADREAC DRA for a product authorized in the EU via MRP, including subsequent VARs and RENs.

The basis for the assessment for the DRAs is the original dossier, which was submitted and approved for MRP in EU by RMS and Concerned Member States (CMSs).

The procedure offers the possibility of harmonizing of the SmPC, PIL and the documentation of the MP authorized in EU MSs via MRP with CADREAC MSs.

It should be also taken into account that harmonization of innovative products authorized by CADREAC DRAs with those authorized in EU is a condition for harmonization of their generics in the future (cf. 7.9, cf. 7.10).

The simplified CADREAC procedure has entered into force on 3rd May 2001.

The mentioned documents (cf. 7.9, cf. 7.10) describing the simplified CADREAC procedure for products authorized in EU via MRP are divided into the following sections:

- *"Background*
- *Principles*
- *Responsibilities of concerned parties*
- *Procedure with Variant I and II*
- *VARs of MA of the MP, which have been authorized following the DP in the EU*
- *Retrospective inclusion of EU DP MP in the CCP*
- *Annexes 1 – 3"*

As mentioned before, the focus of the master thesis lies in the comparison of the NP (cf. 7.11) and the simplified CADREAC procedure for products authorized in EU via MRP (cf. 7.9, cf. 7.10), therefore the chapters *"VARs of MA of the MP, which have been authorized following the DP in the EU"* and *"Retrospective inclusion of EU DP MPs in the CCP (in force since 10th June 2001)"* are not covered here.

2.1.1 Principles of the simplified CADREAC procedure

Before starting with the description of the procedure itself the principles of the procedure and the responsibilities of the concerned parties are described for a better understanding of the procedure.

The basic principle of the CADREAC procedure is the mutual recognition of the EU MRP, i.e. the recognition of the assessment of the RMS (and CMSs) in EU. The scope of the CADREAC procedure is to offer a possibility of a procedure which can be used by any CADREAC DRA for granting a MA of a MP, which has been authorized in the EU MSs following the MRP including subsequent VARs and RENs. The assessment of the RMS can be assumed to be relevant for CADREAC area because it can be expected that differences in medical practice between the EU MSs and CADREAC area are generally not of major importance for public health (cf. 7.9, cf.7.10)

The use of the CADREAC procedure is not mandatory, but voluntary. The applicant and the CADREAC DRAs can decide whether to use the CADREAC procedure or not. The simplified procedure as such is initiated by the applicant (RMS MAH or headquarter of company) with the submission of an application for MA to a CADREAC DRA with an additional procedure specific documentation (cf. 7.9, cf. 7.10).

The CADREAC DRA specifies individually which products could be subjects to the prodedure and there are in principle three options depending on the respective country which products can be included in the CADREAC procedure (cf. 7.9, cf. 7.10):

1. *„Only products which are submitted with full dossiers for DP in the EU MSs and submitted for the simplified procedure to CADREAC DRA also with full dossier and subsequently for their line extensions*
2. *In addition to products mentioned under 1. also line extensions of products based on a full dossier, which passed DP, but of which the 1st product in the line is not harmonized in the country of the respective CADREAC DRA - simplified procedure applied on the line extension, can therefore start only after harmonization of the 1st product in the line, achieved by VARs,*
3. *All products submitted for DP, including generics.“*

The applicant has to ensure the identity of the dossier and SmPC submitted, as well as identical post-approval development, urgent safety measures and VARs of the product in the EU-MSs and in the countries of the CADREAC Concerned Member States (C-CMSs).

The only acceptable differences in CADREAC procedure are the name of the MP and name of the MAH compared to MRP. In addition, it is not necessary to apply for all package sizes

in the C-CMSs which have been applied for and which are authorized in the CMSs. Legal status of the product remains the national decision of the C-CMSs.

The RMS has the duty to provide the updated assessment report (AR) to the applicant or to respective CADREAC DRA directly.

In addition, CADREAC DRA concerned should be provided with all necessary information also in the post-approval phase (e.g. rapid alerts, urgent safety restrictions) via the applicant or directly by the RMS, based on the declaration on information sharing of the RMS MAH (see appendix 8.1). In each EU-MS and in the CADREAC DRAs, contact points have been established for communication.

If questions or concerns to the EU-RMS AR are raised by the CADREAC DRA, additional documents to the dossier may be required by the CADREAC DRA from the applicant, or additional assessment according to the usual NP may be carried out.

It remains a national C-CMS decision to establish a special track for processing these MAAs in the CADREAC DRA with possible acceleration.

National legislation of each CADREAD country is applicable for all requirements of dossier submission, e.g. number of copies, samples, acceptance of electronic dossiers and regulation of fees.

The CADREAC DRAs keep their responsibilities for granting MAAs, approving VARs and RENs and supervising safety measures within their respective territories according to their national legislations and national laws (cf. 7.9, cf. 7.10).

Each CADREAC DRA can decide about the startpoint of the procedure. The procedure will be started after submission of the MAA to the CADREAC DRA. There is the possibility to start the procedure at any time after completion of the respective (first) recognition procedure by the EU CMSs, i.e. after the day 90, (further on described as variant I) or to start the procedure already when the MA is granted only by the RMS (further described as variant II).

It is allowed that experts of CADREAC DRA concerned or CADREAC observers participate in a break-out session, based on a written agreement of the applicant in the RMS, in case that an application is pending at a CADREAC DRA and EU-CMSs in parallel (variant II).

The CADREAC DRA decides whether just one or both of the described variants are practized. The submission must comply with the administrative requirements of the C-CMS.

The specific national requirements of each CADREAC DRA are listed in the Annex 3 - *„Table of specific national requirements of CADREAC DRAs“* of the document *“Procedure on the granting of MAs by CADREAC DRAs for human MPs already authorized in EU MSs following the DP”* (cf. 7.9, cf. 7.10) (please refer also to section 2.3) (see appendix 8.3).

Also, the scope of the procedure, the timing of the submission, the expected handling net time, the language of the dossier, the number of copies to be submitted, the requirements concerning electronic submission, the need of samples and/or substances, the fees and the date of implementation are mentioned for each CADREAC country.
It should be emphasized that variant II was only possible in Slovakia but presubmission consultation was required. In all other CADREAC and Ex-CADREAC (new EU-MSs) countries only variant I is/was possible – submission of the MAA any time after completion of the respective MRP, when an updated AR is available - whereas in Czech Republic, Hungary and Latvia variant I was only possible after day 90 of the MRP. Therefore for most of the CADREAC countries only variant I is feasible.

2.1.2 Responsibilities of the concerned parties

One other important aspect for the CADREAC procedure are the concerned parties which are involved in the CADREAC procedure - which are the applicant/MAH in the CADREAC area, the MAH in the RMS, the CA of the RMS and the CADREAC DRA - and their different jobs and responsibilities in the CADREAC procedure.

The applicant/MAH in the CADREAC area has to ensure that the dossier submitted is identical to the dossier submitted in the CMSs.
He has to take care that the declaration according to Annex 1 (cf. 7.9, 7.10) (see appendix 8.1) will be available also from restricted part of European Drug Master File (EDMF) holder (manufacturer of active substance), if EDMF procedure has been used.
The applicant/MAH is responsible that the MP will be kept identical in the post-marketing phase and that all information on the course of the MRP as required for variant II will be submitted to the CADREAC DRA in time.

The MAH in the RMS has to sign a declaration on the information sharing and participation of experts of CADREAC DRA concerned or observers in break-out sessions of the Mutual Recognition Facilitation Group (MRFG), if appropriate (cf. 7.9, cf. 7.10, Annex 1) (see appendix 8.1) and has to sent this declaration to the national authority of the RMS and a copy to the CADREAC DRA.

The CA of the RMS has to make available the updated AR and if necessary post-approval information (like rapid alerts, urgent safety restrictions) to MAH in the EU or CADREAC DRA directly.
RMS should provide CADREAC DRA concerned with all necessary information also in the post-approval phase (like rapid alerts, urgent safety restrictions) via the applicant or directly, based on the declaration on information sharing of the RMS MAH. Contact points in each EU-MS and in the CADREAC DRAs have been established for communication.

The CADREAC DRA concerned has to ensure to keep information submitted and generated during this procedure confidential and has the duty to send the report on the outcome of the procedure in the C-CMSs to the RMS (cf. 7.9, cf. 7.10, Annex 2) (see appendix 8.2) and a copy of the report to the CADREAC secretariat. In case of disagreement or modification other than defined, the report will include a justification and will be also sent to all CADREAC DRAs.

2.2 Description of the procedure for getting a MA

Accordingt to the document *„Procedure on the granting of MAs by CADREAC DRAs for human MPs already authorized in EU MSs following the DP"* (cf. 7.9, cf. 7.10) the initiation of the CADREAC procedure is done by the RMS MAH. Practically, it is also possible that the headquarter of a company initiates the procedure, especially in cases where local affiliates are MAH in RMS. The initiator of the procedure notifies the EU-RMS that a MAA will be submitted in one or more C-CMSs. In addition, the initiator of the procedure - RMS MAH or the headquarter - submits a written declaration to the CA of the RMS wherein he declares that the CA of the RMS may make available to the CADREAC DRA any information regarding quality, safety and efficacy of the concerned product(s) and in the case that variant II is used he agrees with the participation of the CADREAC expert in the break out session (see appendix 8.1).
It should be considered, that the CADREAC procedure itself and the evaluation of dossier are not described in detail in the CADREAC procedure document (cf. 7.9, cf. 7.10). It can be expected that the evaluation of the dossier is done in the same way as done for the NP in Romania (please refer to Section 3.2. „Description of the procedure").
As mentioned before, the CADREAC procedure for a product authorized in EU via MRP offers two different variants which can be used to apply for a MA. In the following these two different variants are described.

2.2.1 Description of the procedure for getting a MA - Variant I - after finalization of MRP

For variant I of the simplified procedure the application for MA is submitted any time after completion of the respective MRP, before or when an updated AR is available.

The documents which have to be submitted by the applicant for this variant I, which are listed in the *"Procedure on the granting of MAs by CADREAC DRAs for human MPs already authorized in EU MSs following the DP"*(cf. 7.9, 7.10), are:

- *„Application form (the appropriate national application form for the MA of a MP together with administrative data and samples required by the CADREAC DRA concerned)*
- *Dossier identical with the dossier submitted in the EU-CMSs in MRP*
- *Consolidated list of questions raised by CMSs within the MRP and applicant's response document in MRP (day 65 responses to questions raised by CMSs within the MRP) and later responses*
- *Updated AR of RMS, including harmonized SmPC (if EDMF procedure has been used, the AR on the restricted part should be requested from RMS directly)*
- *If there is only RMS AR available, the applicant should provide information on the MRP:*
  - ➔ *List of CMSs*
  - ➔ *History of the MRP*
  - ➔ *Break out session minutes, if applicable*
  - ➔ *Information about the reasons for withdrawal(s)*
  - ➔ *The letter of RMS about the completion of the procedure with SmPC attached*
- *If VARs have been accepted after conclusion of the MRP, a list of these VARs has to be part of the submission; the documentation submitted in the EU-MSs to support these VARs shall be annexed to the original dossier*
  - ➔ *VAR AR(s), if applicable*
- *In case the application in the C-CMS is submitted later than 9 months after the authorization in EU-RMS and concerns a new active substance, the latest available Periodic Safety Update Report (PSUR)*
- *List of post-authorization commitments imposed in MRP and the status of their fulfilment, if any*
- *Declaration of the applicant that*

- ➔ *He will deal with CADREAC DRA similarly as he or relevant MAH deals with CAs of EU-MSs, especially he will keep the product authorized by the CADREAC DRA identical with the EU-MSs, i.e. in the post-authorization phase he will notify and implement all urgent safety measures simultaneously in the EU-MSs and the C-CMSs and he will submit and implement all VARs, once accepted in the EU-MSs, without unnecessary delay*
- ➔ *Dossier submitted to the C-CMSs is identical to the dossier submitted in the EU-CMSs for MRP, including all information submitted to support any VAR which has been applied for and accepted at the time of submission of the application in the C-CMSs as well as information concerning post-authorization commitments, if any (i.e. the documentation reflects the situation of the product, which is in the EU-MSs at the time of submission of the application in the C-CMSs)*
- ➔ *The submitted proposal of SmPC in local language is the translation of the SmPC as last approved in MRP*

- *Declaration of the MAH in RMS and if necessary, also of the holder of restricted part of EDMF"*

The evaluation of the dossier and the assessment procedure remains country specific. Each CADREAC DRA will review the dossier submitted for simplified procedure individually.
Each CADREAC DRA will create an AR and will send the report of the outcome to the RMS and a copy to the CADREAC secretariat.

2.2.2 Description of the procedure for getting a MA - Variant II – in parallel with MRP

For variant II, the MAA is submitted after the RMS issued the AR and before the finalization of the MRP.
Therefore it is advisable that the applicant consults the relevant CADREAC DRA before the submission in order to clarify any open issues.
Due to the timepoint of submission of the MAA, for variant II are less documents necessary because some of the documents requested for variant I are not yet available for variant II (like updated AR including harmonized SmPC, consolidated list of questions raised by CMSs and the consolidated response of the applicant, PSUR, VARs and AR for VARs).
The documents which have to be submitted by the applicant for this variant II, which are listed in the *"Procedure on the granting of MAs by CADREAC DRAs for human MPs already authorized in EU MSs following the DP"* (cf. 7.9, 7.10), are:

- *„Application form (the appropriate national application form for the MA of a MP together with administrative data and samples required by the CADREAC DRA concerned)*
- *Dossier identical with the dossier submitted in the EU-CMSs in MRP*
- *AR of RMS including SmPC as approved in the RMS in English language (if EDMF procedure has been used, the AR on the restricted part should be requested from RMS directly)*
- *Declaration of the applicant that*
  - ➔ *He will deal with CADREAC DRA similarly as he or relevant MAH deals with competent authorities of EU-MSs, especially he will keep the product authorized by the CADREAC DRA identical with the EU-MSs, i.e. in the post-authorization phase he will notify and implement all urgent safety measures simultaneously in the EU-MSs and the C-CMSs and he will submit and implement all VARs, once accepted in the EU-MSs, without unnecessary delay*
  - ➔ *Dossier submitted to the CADREAC DRA is identical to the dossier submitted in the RMS and EU-CMSs for MRP, if applicable*
  - ➔ *He will inform the CADREAC DRA on each step of the relevant MRP*
- *Copy of the declaration of the MAH in RMS and if necessary, also of the holder of restricted part of EDMF“*

The applicant provides the CADREAC DRA with the information on and all steps of the MRP in due time as defined for MRPs in the *”Best practice guide for MRP”* as currently revised (cf. 7.12).

The assessment procedure remains country specific. Each CADREAC DRA will review the dossier submitted for simplified procedure individually.

Each CADREAC DRA will create an AR and will send the report on the outcome to the RMS and a copy to the CADREAC secretariat.

2.3. Country specific issues of the CADREAC procedure for getting a MA – Romania

As mentioned before, the document *“Procedure on the granting of MAs by CADREAC DRAs for human MPs, already authorized in EU MSs following the DP”* (cf. 7.9) describing the CADREAC procedure for products authorized in EU via MRP, is also implemented in the Romanian national legislation as *”Decision No. 8/04.05.2001 regarding the approval of procedure on the granting of MAs by CADREAC CAs for MPs for human use, already*

authorized in EU MSs following the DP" (cf. 7.10). The content of both documents concerning the CADREAC procedure is identical. The date of implementation of the CADREAC procedure in Romania was 3rd May 2001, the publishing date of the guideline of CCP.

There is no harmonization concerning the administrative data, which are requested for a CADREAC procedure. Each CADREAC DRA has its own national application form and its own requirements concerning administrative data. Therefore, the compilation of the administrative data for the CADREAC procedure remains also country specific and is based on the national requirements of each CADREAC country. These are listed in the Annex 3 - *„Table of specific national requirements of CADREAC DRAs"* of the document *"Procedure on the granting of MAs by CADREAC DRAs for human MPs already authorized in EU MSs following the DP"* (cf. 7.9, cf. 7.10) (see appendix 8.3 and 8.4).

Therein the scope of the procedure, the timing of the submission, the expected handling net time, the language of the dossier, the number of copies to be submitted, the requirements concerning electronic submission, the need of samples and/or substances, the fees and the date of implementation of the CADREAC procedure are mentioned for each CADREAC country.

For Romania the scope of the procedure is *„only products submitted for MRP in MSs with full dossier and submitted for the simplified procedure to the National Medicines Agency (NMA) also with full dossier and subsequently for their line extensions (new pharmaceutical formulations, new concentrations)"* (cf. 7.9, cf. 7.10, point 3.1 of principles).

This means that in Romania the CADREAC procedure is only possible for one of the three options as described in the original guideline *"Procedure on the granting of MAs by CADREAC DRAs for human MPs, already authorized in EU MSs following the DP"* (cf. 7.9), which products can be included in the CADREAC procedure (cf. 7.9, cf. 7.10, principles; point 3.1.; please refer also to page 16, no. 1).

In addition in Romania, as mentioned before, only variant I of the simplified procedure is possible, which means the MAA is submitted any time after completion of the respective MRP, when an updated AR is available.

The expected handling net time for Romania is 6 months, but there is usually a delay of 3 to 4 months due to the high workload of the DRA.

The languages which are acceptable for the Romanian authority (NMA) are Romanian and English and therefore the dossier and documents can be submitted in one of these languages.

The documentation should be submitted in one fold, with the exception of the updated AR of the RMS, the final MRP SmPC, proposed Romanian SmPC, PIL and labelling, which are requested to be submitted in two folds.
Concerning electronic submission it is possible to submit the dossier in Pharmbridge-DAMOS format, CD-ROM, together with paper documentation of identical content.
The final approved versions of the (Romanian) SmPC and PIL in the Romanian language can be submitted on a 3,5 inch floppy disk, using Word format.
Two samples of the MP presented in the outer packaging are requested. In addition, reference standard has to be submitted if the testing procedure refers to a reference standard.
In Romania the fees for a MA according to CADREAC procedure are 1.500 USD.

2.4 Evaluation of the CADREAC procedure for getting a MA

2.4.1 General advantages and disadvantages of the CADREAC procedure

In general, the advantages for the applicant to use the simplified CADREAC procedure are:

1. Duration of procedure
   - Simplified procedure takes only a few months to get a MA (fast MA procedure)
     ➔ CADREAC procedure takes between 4 and 12 months depending on the review time in each country (shortest country is Bulgaria with 120 days, Romania needs 6 months (usually there is a delay of 3 to 4 months) and the longest country was Hungary with 12 months)

2. Evaluation of the dossier
   - Evaluation of the dossier is quite easy (for the authorities) and can be made quite fast (at the authorities) if using the simplified CADREAC procedure
     ➔ Because documents like EU AR are available (wherein the results of the evaluation of the dossier by the RMS are described), for variant I also consolidated list of questions and answers are available
     ➔ Only a few or no questions/objections occur from the authorities if applicant uses the simplified CADREAC procedure because pre-evaluation documents like EU AR are available

3. Harmonization of documentation, SmPC and PILs
   - The applicant /MAH has the possibility of harmonization of the documentation and the labeling (SmPC, PIL) of a MP authorized in EU MSs and CADREAC countries

4. Life-cycle management
   - Handling of life-cycle management (e.g. handling of any changes and VARs) is easier because of identity of dossier and labeling documents with EU

5. Integration of national authorized product in an existing MRP
   - After joining the EU, integration in the EU MRP was (and will be) possible because of the identity of the documentation, SmPC and PIL without doing a new complete MRP (90 day procedure):
     ➔ So called „administrative MRPs“ (30 day procedure) were (and will be) possible for products which were authorized in the CADREAC countries via simplified procedure to include CADREAC countries into the MRPs

The disadvantages for the applicant to use the simplified CADREAC procedures are:

1. Flexibility
   - The applicant/MAH has little flexibility because of commitment to handle the dossier and labeling documents equivalent/identical to EU by submitting the requested documentation and declarations (please refer to section 2.2.1 and section 2.2.2)
     ➔ If using the simplified CADREAC procedure the applicant/MAH has to submit the identical documentation and labeling documents as submitted and approved in EU via MRP
     ➔ If using the simplified CADREAC procedure the applicant/MAH can only apply for the same indications as approved in EU
     ➔ If the CADREAC procedure is used, the applicant/MAH can apply for a MA only in the dossier format in which the MRP dossier is available (either in old Notice to Applicants (NtA)-format or in new Common Technical Document-format (CTD)-format)

2. Evaluation of the dossier
   - DRAs in CADREAC countries do not have and will not make a complete assessment of the dossier by their own because documents like EU AR and the consolidated list of questions and answers are available
     ➔ Disadvantage has to be expected especially for products for which difficulties occur during MRP (like restriction of indications or expansion of adverse effects or withdrawals of countries from the procedure)

3. Life-cylce management
   - The applicant/MAH has the obligation to handle the life-cycle management (e.g. handling of any changes and VARs (because of identity of dossier and labeling)) identical to EU

4. Advantage for generics - Harmonization of SmPC and PILs
   - For generic companies it is easier to apply for and receive MAs in the CADREAC countries due to the fact that the prerequisite for generics - the harmonization of SmPC and PILs - is done by the originators

5. Use of simplified CADREAC procedure not always possible
   - Simplified CADREAC procedures can only be used for products which are authorized in EU via CP or MRP. This means especially for older products which have been authorized in EU via NP (before 1995) simplified CADREAC procedures are not possible

6. Costs of the procedure
   - Simplified CADREAC procedures are quite expensive (more expensive than NPs); costs approx. 1.500 USD

2.4.2 Comparison between Variant I and II of the CADREAC procedure for getting a MA

As mentioned in section 2.2. „*Description of the procedure for getting a MA*“, the CADREAC procedure offers two different variants which can be used for getting a MA.

The main difference between variant I and II is the timing for submission of the application in the C-CMSs. Whereas variant I can only be used after finalization of the MRP in EU (submission any time after completion of the respective MRP, before or when updated AR is available), variant II can already be used after the RMS has issued the AR which means in parallel with the MRP in EU.

As mentioned before, variant II was only possible in Slovakia but presubmission consultation was required. In all other CADREAC and Ex-CADREAC (new EU MSs) countries only variant I is/was possible – submission of the MAA any time after completion of the respective MRP, when an updated AR is available - whereas in Czech Republic, Hungary and Latvia variant I was only possible after day 90 of the MRP. Therefore for most of the CADREAC countries only variant I is feasible and the advantage of time using variant II is only valid for Slovakia.

An advantage of using variant I is that the documentation and labeling documents approved in EU (by MRP) are used for applying of the MA in the CADREAC countries and the availability of the updated AR and the consolidated lits of questions and answers. Therefore, for variant I the risk of requests of the authority to make changes in the documentation or labeling documents is very low.

For variant II the approval of the MAA in the CADREAC countries will be received earlier than for variant I because variant II is running in parallel with the MRP which may represent an advantage.

On the other hand, for variant II it is necessary that the applicant will inform the CADREAC DRA on each step of the relevant MRP and also on the changes in the SmPC during the MRP as described in the *”Best practice guide for MRP”* as currently revised (cf. 7.12). The applicant should also provide - at the end of the MRP - the final SmPC to the CADREAC countries.

This means that the workload for the applicant is higher compared to using variant I and the applicant has to be in close contact with the CADREAC DRAs. Also the risk of requests of the CADREAC authorities to make changes in the documentation or labeling documents is higher than for variant I.

The documents which have to be submitted for both variants are nearly identical. The differences are due to the time of submission between variant I and II. For variant I are therefore more documents requested like (cf. 7.9, cf. 7.10):

- *„Consolidated list of questions raised by CMSs within the MRP and applicant's response document in MRP (day 65 responses to questions raised by CMSs within the MRP) and later responses*
- *Updated AR of RMS, including harmonized SmPC (if EDMF procedure has been used, the AR on the restricted part should be requested from RMS directly)*
- *If there is only RMS AR available the applicant should provide information on the MRP:*
  - ➔ *List of CMSs*
  - ➔ *History of the MRP*
  - ➔ *Break out session minutes, if applicable*
  - ➔ *Information about the reasons for withdrawal(s)*
  - ➔ *The letter of RMS about the completion of the procedure with SmPC attached*
- *If VARs have been accepted after conclusion of the MRP, a list of these VARs has to be part of the submission; the documentation submitted in the EU-MSs to support these VARs shall be annexed to the original dossier*
  - ➔ *VAR AR(s), if applicable*
- *In case the application in the C-CMS is submitted later than 9 months after the authorization in EU-RMS and concerns a new active substance, the latest available PSUR*
- *List of post-authorization commitments imposed in MRP and the status of their fulfilment, if any"*

As mentioned, before, for variant II it is necessary that the applicant will inform the CADREAC DRA on each step of the relevant MRP and also on the changes in the SmPC during the MRP. The applicant should also provide at the end of the MRP the final SmPC to the CADREAC countries.

All other issues - especially the procedures itself - are identical between variant I and II.
The assessment procedure remains country specific. Each CADREAC DRA will review the dossier submitted for simplified procedure individually.

Each CADREAC DRA will create an AR and will send the report of the outcome to the RMS and a copy to the CADREAC secretariat.

III. NATIONAL PROCEDURE IN ROMANIA

3.1 General overview

The legal background for the national MA procedure in Romania lies down in the *"DECISION No. 1/17.01.2003 regarding the approval of Regulations on MA and surveillance of MPs for human use (Romania) and its Annex 1: Regulations on MA and surveillance of MPs for human use"* (cf. 7.11).

In this decision the NMA Scientific Council declares that "*regulations on MA and surveillance of MPs for human use are approved in accordance with the annexes that are part of the present decision"* (Art. 1 of the decision No. 1/17.01.2003).

It further says that the decision and its annexes are legally binding. The decision replaces "*Decision No. 27/2000 regarding the approval of regulations on MA and surveillance of medicinal products for human use and of the Norms on the documentation required for MA or renewal of MA of medicinal products for human use"* (cf. 7.13) as mentioned in Art. 2.

In Art. 3 the NMA Scientific Council explains, that "*the present decision will be approved through Order of the Minister of Health and Family, will be notified to the European Integration Ministry and will be published in the Official Monitor, Part I.*"

The 4 annexes of the decision describe "*the regulations on MA and surveillance of MPs for human use (including MAAs, REN, VARs), the application form for MAAs/RENs of MPs for human use, the analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of MPs and the norms regarding the documentation required for MA or REN of MA of MP for human* use." The 4 annexes are divided in the several chapters (cf. 7.11).

The purpose of the decision No. 1/17.01.2003 and its annexes is to describe the regulations on MA and surveillance of MPs for human use (including MAAs, REN, VARs) (cf. 7.11).
The regulation describes the procedures for getting a MA via NP, the REN procedure, the VAR procedure, etc. and it also describes in detail the requirements and timelines for each procedure (e.g. documents needed).

Chapter 1 of annex 1 (cf. 7.11) describes the general provisions for marketing a MP in Romania.
In Art. 1 of the Chapter 1 of annex1 explains that "*the present regulations are elaborated in accordance with Chapter II "MA of the MPs" and Chapter V "Surveillance of MPs" from*

Law No. 336/2002 for approval of Emergency Ordinance No. 152/1999 regarding MPs for human use."

In Chapter 1 of annex 1, it is explained that before MPs for human use can be marketed, the MA has to be granted by the NMA.

NMA grants only MAs, which fulfill the requirements concerning quality, safety and efficacy, which are defined in the regulation (annex 1 of the decision No. 1/17.01.2003 (cf. 7.11)).

This is applicable for MPs, which contain chemical substances, radio pharmaceutical products, biological products, phytotherapeutic products, homeopathic products and products obtained trough biotechnology.

The applicant for a MA in Romania has to be Romanian manufacturer or foreign manufacturer with representative office in Romania or Romanian juridical person empowered by the manufacturer, with specialized personnel employed (physicians or pharmacists).

It is for NMA to decide on the acceptability of dossiers. NMA also decides about granting, changing, suspension or withdrawal/rejection of MA of a MP for human use. The decisions are made in accordance with the provisions of the present regulation (annex 1 of the decision No. 1/17.01.2003 (cf. 7.11)).

The annex 1 of the decision No. 1/17.01.2003 offers the NMA also the possibility -depending on necessities - to contact external experts for the assessment of the dossier, especially for the evaluation of chemical-pharmaceutical and biological, pharmaco-toxicological or clinical documentation, with regard to MA.

3.1.1 Principles of the procedure

In the following the chapters II to VI of the annex 1 of the decision No.1/17.01.2003 (cf. 7.11) will be described more detailed because these are the important parts of the regulation for this master thesis.

The Chapter II of the annex 1 of the decision No.1/17.01.2003 *"Submission of applications for authorizations"* (cf. 7.11) describes the different types of applications and the requirements concerning requested documentation and samples for them in order to start the MA procedure for MPs for human use.

The applicant has to submit to the NMA an application form as presented in annex 2 (section B) of the decision No.1/17.01.2003 (cf. 7.11) in order to start the MA procedure for MPs for human use. In addition, the documentation as mentioned in annex 3 (section C) of the regulation and presented in accordance with the provisions from annex 4 (section D) should be submitted (cf. 7.11). At the moment, the dossier and documents are requested in the old

NtA-format (according to the old Notice to Applicants) as explained in Section D (Annex 4) (cf. 7.11). But the NMA also accepts the CTD-format, although it is not yet mentioned in the decision No. 1/17.01.2003 and its annexes (cf. 7.11).

Four different types of applications (stand alone applications, informed-consent applications, bibliographic applications and generic applications) and related to dossier requirements are described.

In principle the applicant has four possibilities to apply for a MA:

1. **A stand-alone application**
   - ➔ Submission of a full dossier (Part I to IV (old NtA-format) or Module 2 to 5 (new CTD-format))
2. **An informed-consent application** (application with reduced documentation based on "informed-consent")
   - ➔ MP is essentially similar to a MP already authorized in Romania and the MAH of reference product consents that for the purpose of the respective product examination to refer to its product pharmacological-toxicological and/or clinical documentation
3. **Bibliographic application** (application with reduced documentation based on detailed scientific bibliography)
   - ➔ MP constituent(s) have a well established medicinal use, with recognized efficacy and an acceptable safety level, with the support of detailed scientific bibliography
4. **A generic application** (application with reduced documentation based on the proof of bioequivalence where applicable, with the original/reference product = application for generic products)
   - ➔ MP is essentially similar (proved through bioequivalence studies, where applicable) to a MP which was authorized in Romania based on a complete dossier (original product/reference product for Romania) and which is no longer covered by patent protection

Based on the type of application the documentation to be submitted is different.

For a stand-alone/independent application (e.g. for new chemical entities) the supporting documentation of an application for a new chemical entity should contain (Art. 9,1 of cf. 7.11):

"a) Name and permanent address of the applicant and manufacturer if applicable;

b) Trade name of the MP;

c) Qualitative and quantitative characteristics of all the constituents of the MP named in usual terminology, but excluding empirical chemical formulae, with mention the INN recommended by World Health Organization (WHO), if any;

d) Description of manufacturing method;

e) Therapeutic indications, contra-indications and adverse reactions;

f) Posology, pharmaceutical form, method and route of administration and expected shelf-life;

g) If applicable, any precautionary and safety measures which should be taken for storage of the MP, its administration in patients and for the disposal of waste products, together with an indication of any potential risks presented by the MPs for environment;

h) Description of control methods used by the manufacturer (qualitative and quantitative analysis of the constituents and the finished product, special tests e.g. sterility tests, tests for the presence of pyrogenic substances, the presence of heavy metals, stability tests, biological and toxicity tests, controls carried out at an intermediate stage of the manufacturing process);

i) Results of:

- *Physico-chemical, biological or microbiological tests;*
- *Toxicological and pharmacological tests;*
- *Clinical tests*

j) A SmPC, one or more specimens or mock-ups of secondary and primary packaging of the MP, together with PIL;

k) Documents showing that the manufacturer is authorized to manufacture the MP;

l) Copies of any MA granted by other countries together with the list of countries where the product is under authorization procedure; copies of the SmPC proposed by the applicant or approved by the CAs from other countries; details of any decision to refuse authorization and the reasons for such a decision.

This information should be updated on a regular basis.

In addition to the requirements from item 1 and 2, the application for MA for a radio nuclide generator should also contain the following information:

- *A general description of the system, together with a detailed description of the system components, which may affect the composition or quality of the daughter-radio nuclide preparation;*
- *Qualitative and quantitative characteristics of the eluate or sublimate."*

Whereas for types of application 2 – 4 (informed-consent applications, bibliographic applications and generic applications) in principle no pharmaco-toxicological and clinical data have to be submitted, a complete dossier containing also Part III and IV (Module 4 and 5) is required for a stand-alone application.

In addition, for bibliographic applications it is necessary to show the recognized efficacy and the acceptable safety level with support of detailed scientific bibliography and references to published data.

For informed-consent, bibliographic and generic applications, also results of appropriate toxicological and pharmacological tests and/or appropriate clinical trials must be provided if the MP is intended for a different therapeutic indication than other MPs available on the Romanian market or is to be administered by different routes or in different doses.

For products containing known substances not yet used in combination for therapeutical purposes, the results of toxicological and pharmacological tests and clinical trials relating to that combination must be provided without being necessary to present data regarding each individual constituent.

Art. 10 of Chapter II of the Annex 1 describes the requirements for the documents as requested in Art. 9.1 (cf. 7.11), the "*description of control methods used by the manufacturer"* and the expert reports to be presented for the pharmaceutical-chemical-biological, the pharmaco-toxicological and the clinical documentation.

It is required that the documents mentioned at Art. 9, 1 letters h ("*description of control methods used by the manufacturer"*) and i *("the results of physico-chemical, biological or microbiological tests, toxicological and pharmacological tests and clinical tests"*) and at Art. 9,2 letter a ("*results of pharmaco-toxicological and clinical tests are not required for informed-consent, generic and bibliographic applications"*) have to be written by experts having the necessary technical and professional qualifications. The experts are obliged only to perform tasks falling within their specializations (analytical chemistry, pharmacology or similar experimental sciences, clinical trials) and to describe objectively the results – qualitatively and quantitatively.

The experts have to present their observations and to express clearly their opinion, especially on the following aspects:

"- In the case of the analyst, whether the MP is consistent with the declared composition, presenting any substantiation of the control methods used by the manufacturer;

- *In the case of the pharmacologist or the specialist with similar experimental competence, the toxicity of the MP and the pharmacological properties observed;*
- *In the case of the clinician, whether he has been able to ascertain effects on persons treated with the MP, corresponding, to the data presented by the applicant in accordance with the provisions of art. 2, whether the patients tolerate the MP well, the posology the clinician advises and the contra-indications and the adverse reactions"*

The experts should make a critical assessment of the available data.

The *"description of control methods used by the manufacturer"* and the expert reports to be presented for the pharmaceutical-chemical-biological, the pharmaco-toxicological and the clinical documentation have to be signed by the expert who has written the document.

In Art. 11 the requirements for samples of the finished product are presented.

In general two samples of the finished product are requested, presented in the packaging that follows to be marketed or in mock-ups of the packaging (samples for demonstration purposes). The applicant has the duty to present the final packaging to the NMA after manufacturing the first production batch after the granting of the MA.

In some cases, which are in detail mentioned in decision 24/2002 (cf. 7.14), the NMA Scientific Council requested samples for quality control tests. Samples of the finished product (presented in the packaging that follows to be marketed or in mock-ups of the packaging) in sufficient quantities are requested to allow the verification of all quality parameters from the quality specification and in accordance with the methodology presented in the chemical, pharmaceutical and biological documentation. In addition, also reference substances, supplemental reagents (where appropriate), degradation products (where appropriate) and impurities (where appropriate) are requested for quality control testing.

If more than one pack size exists for one MP, the control tests will be done only with the smallest pack size. In addition, for the other pack sizes two samples of each other pack size are requested for demonstration purposes.

A separate application has to be submitted for each different pharmaceutical form and strength of a MP presented under the same trade name.

The chemical-pharmaceutical and biological documentation has to be submitted in two folds whereas the other documentation should be submitted in one fold.

The documentation for imported MPs can be submitted in Romanian, English or French.

Art. 16 and Art. 17 clarify the authorization fees:

*"**Art. 16.** - (1) The authorization fee established by Government Decision and the authorization tariffs, established by Decision of the NMA Administrative Council and published in the Informative Bulletin of the NMA, are paid at the submission of the application.*

(2) If control laboratory performance was required, the tariffs for laboratory control established through Decision of the NMA Administrative Council and published in the Informative Bulletin of the NMA are paid at the end of laboratory control.

(3) If needed, at the end of the evaluation procedure, a regularization of the fee and the tariff is done.

***Art. 17. -** The stipulations from art. 16 do not apply for products submitted to the NMA prior 1 July 2000; for these, the payment of the authorization fee and tariff and also the tariff for laboratory control is done at the end of authorization procedure."*

3.1.2 Responsibilities of the concerned parties

One aspect for the NP which should be taken into account are the concerned parties involved in the NP - which are the applicant/future MAH in Romania and the NMA Scientific Council and their different responsibilities.

Each of these parties has other responsibilities within the NP, which are important to know.

The applicant/future MAH in Romania will guarantee that the dossier submitted to NMA fulfils the national requirements according to the different types of applications (stand-alone, informed-consent, generic, bibliographic applications)

He has to ensure that the dossier contains all documents mentioned in Annex 1, Chapter II, Art. 9 depending on the type of application and in the Annex 4 (Section D) (cf. 7.11).

He has to take care that the declaration (letter of access) will be available also from restricted part of EDMF holder (manufacturer of active substance), if EDMF procedure has been used.

One other duty of the applicant/future MAH in Romania is the payment of fees, which he is responsible for.

Besides, the applicant/ future MAH in Romania is also responsible for the life cycle of the product (like VARs, RENs).

The NMA Scientific Council will ensure to keep information submitted and generated during this procedure confidential.

The NMA is responsible for issuing the MA certificate together with the SmPC, the PIL and the information regarding the imprinting of primary and secondary packaging approved by the specialty service of the Evaluation-Authorization Department and for sending them to the MAH.

3.2 Description of the procedure

As mentioned in Section 2.2 *"Description of the CADREAC procedure"* the NP, especially the evaluation procedure, is described more detailed than the CADREAC procedure. The decision No. 1/17.01.2003 (cf. 7.11) describes the NP very detailed whereas the CADREAC guideline did not describe the CADREAC procedure in detail. It can be expected that the evaluation of the dossier is done in the same way as done for the NP in Romania.

The description of the NP in Romania can be found in the Annex 1 of the decision No. 1/17.01.2003 *"Regulations on MA and surveillance of MPs for human use"* Chapter III *"Procedure for MA"* (cf. 7.11). First of all, the application for MA accompanied by the documentation and materials mentioned in Chapter II (Art. 8 – 17), corresponding to the type of product for which the authorization is requested, will be submitted to the Receiving Documents-Samples Compartment of the Evaluation-Authorization Department by the applicant.

Then the validation phase (administrative check) is started by Receiving Documents-Samples Compartment checking the availability of all necessary documents and samples. In addition, the arrangement of the documents in the requested order and also the existence of finished product samples, reference substances, impurities and degradation products, where applicable, are verified.

The MAA will be rejected and the reason for this is noted in the receiving register if the documentation and materials submitted by the applicant are not in accordance with the present regulations.

The applicant will pay the authorization fees and tariff according to the national requirements. If the payment of the authorization fee and tariff are done, the money will be transferred in the NMA's account. As soon as the money arrives at the NMA's account, the MAA documentation is distributed to evaluation services and control departments of the NMA.

The control departments of the Evaluation-Authorization Department review the control methods of the finished product and the starting materials as described in Part II

(pharmaceutical-chemical-biological documentation) and they also check the received materials. In case of absences or unclarity, an objection letter - containing all requests of control department - with the request to complete the documentation, is sent to the applicant within 45 days from the date the products have been distributed in the control department.
For the influenza vaccines there exists an exception from this provision, which is described in Art. 22,2 of the annex 1 (section A) of the decision No. 1/17.01.2003 (cf. 7.11): *"Exception from this provision is the influenza vaccine found under the incidence of the authorization/REN process for which the verification of control methodology and of samples is organized in such a way so that the testing is performed in maximum 60 days from their submission date."*

During the evaluation process, the Evaluation-Authorization Department may ask for an inspection of the manufacturing site(s) and/or to the pre-clinical and/or clinical trials site(s) conducted by the inspectors from the Pharmaceutical Inspection Department of the NMA.

The Evaluation-Authorization Department can ask the control department to conduct certain verifications in case unclear issues related to control methodology appear during the evaluation procedure.
In such cases it may be required to submit the necessary quantities of finished product as well as reference substances, additional reagents (if applicable), degradation products (if applicable), impurities (if applicable), in enough quantities to allow laboratory verifications (cf. 7.11, Art. 31).

After the evaluation of the dossier the evaluation services of the NMA issue the complete evaluation report. In parallel, the control departments of the NMA perform the laboratory control tests and present their results.
After NMA has issued the complete evaluation reports for the dossier, the complete evaluation reports and the results of the laboratory tests are presented in the meetings of the Commission for MA, which decides upon the granting of the MA.
The evaluation process of the MAA can be finalized with three different options:

- With the granting, depending on the case, of a final report with requests for completion ⇒ objection letter
- With the granting, depending on the case, of a final report with recommendation for authorization ⇒ granting of MAA

- Of a final report with rejection of the authorization ⇒ rejection of MAA

If the applicant gets a final report with requests for completion, he will have 6 months time from date of receiving the request for answering to all formulated requests.
Should the applicant not answer integrally to all requests the authorization procedure is definitely interrupted (please refer also to page 38).
If the authorization procedure was interrupted in accordance with Art. 6 or 8, the procedure can be resumed by the submission of a new application for MA accompanied by complete documentation, samples of finished product and where applicable samples for control laboratory, reference substances, impurities and degradation products and payment of fees and authorization tariffs, in accordance with provisions from Chapter II.
It is also possible that the applicant can ask for a procedure interruption during the MA procedure.

If the Commission for MA gives a positive opinion for the MA, it has to be checked with the General Administration Departments if all corresponding fees for MA have been paid.
After the confirmation of the General Administration Departments of receiving all the corresponding fees for MA, the MA can be issued.
The MA contains the product identification data, which are:

- Trade name
- Pharmaceutical form
- Strength
- Qualitative and quantitative composition
- Manufacturer
- Manufacturing site
- MAH
- Anatomical Therapeutic Chemical (ATC) code
- Classification for supply
- Size of commercial packaging
- Shelf-life

and is accompanied by 3 annexes:

- SmPC
- PIL
- Information on imprinting of primary and secondary packaging approved by the specialty service of the Evaluation-Authorization Department is issued

All MPs, for which MAs are granted, will be entered in the Register of MPs authorized in Romania and receive an authorization number. The number is formed by 3 groups of digits that represent:

- Product authorization number
- Authorization year
- Number corresponding to types of packaging authorized

and should be imprinted on secondary package.

The issued MA is valid for 5 years from the date of it's granting by the NMA and can be renewed for another 5 years at the request of its MAH.

The documentation will not be returned; the NMA will retain this documentation for 5 years.

The whole MA process (validation phase, evaluation process and opinion from the Commission for MA) to finalize the procedure for MA may take at maximum 18 months from the date when the NMA receives the authorization fees as mentioned in Art. 21 (cf. 7.11, Art. 29).
The period to finalize the MA procedure will be prolonged with the time interval in which the completions were transmitted if an objection letter with the request of completion of the documentation was issued.

As it is valid for all MA procedures worldwide, it is also possible that a MA is refused and not granted due to the following reasons (cf. 7.11, Annex 1, Chapter VI, Art. 43):

- *"The MP is harmful under normal conditions of use*
- *The therapeutic efficacy is lacking or the applicant insufficiently substantiates this*
- *The qualitative and quantitative composition is not declared*
- *The documentation submitted to the NMA does not correspond to the provisions of Section C and D, which are part of the present regulations"*

The refusal is announced in writing and an appeal is possible (cf. 7.11, Annex 1, Chapter VI, Art. 43 – 46).

3.3 Evaluation of the national procedure

The NP takes at maximum 18 months from the date of payment of the fees until the MA is granted, as mentioned in Art. 29 of the annex 1 of the decision No. 1/17.01.2003 (cf. 7.11). It may also happen that the NP takes even longer than 18 months due to the high workload of the authority (NMA). Therefore the duration of the NP is quite long and from this point of view the NP is not very comfortable.

At the moment, the dossier and documents are requested in the old NtA-format (according to the old Notice to Applicants) as explained in Section D (Annex 4) (cf. 7.11). But the NMA also accepts the CTD-format, although it is not yet mentioned in the decision No. 1/17.01.2003 and its annexes (cf. 7.11). Mixed dossiers - meaning dossiers where some Parts/Modules are in the old NtA-format and the other Parts/Modules are in the new CTD-format (e.g. Part II is in the new CTD-format and Part III is in the old NtA-format) - are not acceptable for new MAAs. Also, hybrid dossiers - which means that some documents in one Part/Modul are in the old NtA-format and some documents of that Part/Modul are in the new CTD-format (e.g. Part IIA is in NtA-format and Part IIE is in CTD-format) - are also not acceptable for new MAAs.
This means, the complete MAA dossier has to be presented either in NtA or in CTD format. This leads to an additional workload at the companies because for many dossiers neither complete CTD nor complete old NtA dossiers are available at the moment. Due to the fact that since 1st Nobember 2003 CTD-format is mandatory for all submissions (MAAs, RENs and VARs) in EU, a lot of mixed and/or hybrid dossiers are available. Therefore this may also be a disadvantage for the NP.

As mentioned in Annex 1, Art. 5 of Chapter I *"General provisions"* the applicant for a MA in Romania has to be a Romanian manufacturer or a foreign manufacturer with representative offices in Romania or a Romanian juridical person empowered by the manufacturer, with specialized personnel employed (physicians or pharmacists). This means, if a European company wants to apply for a MA in Romania, it cannot be done by themselves, but the company need a subsidiary in Romania or an agent, which is authorized to be the applicant.
As mentioned in section 3.1. *"General overview"*, principally the applicant has four possibilities to apply for a MA (please refer to section 3.1; cf. 7.11, Annex 1, Art. 9):

1. A stand-alone application
2. An informed-consent application

3. Bibliographic application
4. A generic application

Based on the type of application the documentation which has to be submitted is different.
Whereas for variant 2 – 4 no pharmaco-toxicological and clinical data have to be submitted, a complete dossier containing also Part III and IV (Module 4 and 5) is required for a stand-alone application.
The administrative data which has to be submitted are identical for all four types of applications (please refer to cf. 7.11, Annex 1, Art. 9).
This means, that the requirements for the dossier is depending on type of applicant and differ for each type of application. Therefore, depending on the type of application the NP to apply for a MA can be a good possibility, especially for bibliographic applications.

The advantages for the applicant to use the NP are:

1. Flexibility
   - MAH has flexibility because the dossier and labeling documents do not have to be identical to dossier and labeling documents submitted and approved in EU:
     ➔ If using the NP the applicant/MAH can apply e.g. for more and different indications as approved in EU
     ➔ In Romania, the applicant/MAH can apply for a MA also in the old NtA-format and does not have to use a dossier in CTD-format if using the NP

2. Evaluation of the dossier
   - Complete evaluation of the dossier is done by each DRA in the CADREAC countries – in Romania by NMA (National agency has to do a complete evaluation of the dossier by its own which takes quite a lot of time (e.g. EU AR and consolidated list of questions and answers will not be made available))
     ➔ This can be an advantage especially for products for which difficulties occur during MRP (like restriction of indications or expansion of adverse effects or withdrawals of countries from the procedure)

3. Life-cylce management
   - There is no obligation to handle the life-cycle management (e.g. handling of any changes and VARs) identical to EU

4. Advantage for generics - Harmonization of SmPC and PILs
   - The way for generics to get MAs is more complicated due to the fact that the prerequisite for generics (the harmonization of SmPC and PILs) has to be done by themselves and is not done by the originators

5. Costs of the procedure
   - The NPs in the CADREAC countries are cheaper than the CADREAC procedures
     ➔ In Romania, the NP costs 973 USD

6. Date of submission of MAA
   - MAA via NP is possible as soon as the product is authorized in one EU MS (e.g. in the RMS) because of the availability of the Certificate of a Pharmaceutical Product (CPP)
     ➔ Submission of MA earlier than using the simplified CADREAC procedure (variant II or variant I)

7. Required documents for MAA
   - Depending on the type of application (stand-alone, informed-consent, generic and bibliographic application), in Romania, the NP to apply for a MA can be a good possibility, especially for bibliographic applications

The disadvantages for the applicant to use the NPs are:

1. Duration of procedure
   - NPs in general take very long (years) in the CADREAC countries
     ➔ NPs take between 1 and 3 years depending on the CADREAC country
     ➔ In Romania, NP takes at maximum 18 months (Art. 29 of cf. 7.11), but it may also happen that the NP takes even longer than 18 months due to the high workload of the authority (NMA)

2. Evaluation of dossier
   - Complete evaluation of the dossier is done by each DRA in the CADREAC countries – in Romania by NMA (National agency has to do a complete evaluation of the dossier by its own (e.g. EU AR and consolidated list of questions and answers will not be made available))

- More questions/objections from the authorities can be expected if applicant uses the NP because not pre-evaluation data like EU AR are available

3. Harmonization of SmPC and PILs
   - There is nearly no possibility of harmonization of the documentation and the labeling (SmPC and PIL) of a MP authorized in EU MSs and specific CADREAC countries because the evaluation of dossier is a country specific issue

4. Life-cylce management
   - Life-cycle management (e.g. handling of any changes and VARs) is more complicated than for products authorized via simplified CADREAC procedures because of different dossiers have to be kept by company (country specific dossiers) (because of the non-identity of dossiers and labeling)

5. Inclusion of national authorized product in an existing MRP
   - After joining the EU it will be possible to include nationally authorized products into an existing MRP (90 day procedure) by the mean of a repeat use MRP (90 day procedure), but there is no legal obligation to do so ⇒ takes longer than the 30 day „administrative“ MRP for MPs which are already authorized via CADREAC procedure

6. Dossier format requested
   - The complete MAA dossier has to be presented either in NtA or in CTD format, mixed and/or hybrid dossiers are not acceptable
     ➔ This leads to an additional workload at the companies because for many dossiers neither complete CTD nor complete old NtA dossiers are available at the moment

IV. COMPARISON BETWEEN CADREAC PROCEDURE AND NATIONAL PROCEDURE INCLUDING DISCUSSION

The using of the simplified CADREAC procedure for products authorized in the EU via CP or MRP offers the possibility to register a MP in a CADREAC country within a few months.
However, there are several points to be discussed associated with the use of the simplified CADREAC procedure compared to the NP which should be considered for the decision which procedure to use for the MAA of a certain product in the CADREAC countries.
Both procedures - the simplified CADREAC procedure and the NP – have advantages and disadvantages (as mentioned in section 2.4 *„Evaluation of the CADREAC procedure for getting a MA“* and section 3.3 *„Evaluation of the NP*“) which will be discussed in the following.

One advantage for the applicant to use the simplified CADREAC procedures is the benefit of time because this procedure takes less time than the NP for getting the respective MA.
For example, in Romania the NP takes 18 months at maximum (average time approximately 12 months), whereas the simplified CADREAC procedure takes 6 months, but usually there is a delay of 3 to 4 months due to high worklaod of the authority. The benefit of time for Romania is obviously 6 – 12 months.

Another aspect to use the simplified CADREAC procedure is the possibility of harmonization of the documentation and the labeling documents (SmPC and PIL) of a MP authorized in EU MSs and CADREAC countries.
The applicant has to submit for a simplified CADREAC procedure the documentation and labeling documents identical to those approved in EU. In this case one identical dossier and identical labeling documents are approved in EU MSs and CADREAC countries.
This harmonization of labeling documents (SmPC and PIL) is a prerequisite for generics done by the originators. Thus, generics can apply for, can get easier MAs, and can come earlier and easier to the market which is a clear advantage for generics and a big disadvantage for originators. If the product is authorized via NP in each CADREAC country the labeling documents (SmPC and PIL) are normally not harmonized. In this case, the way for generics to get MAs is more complicated due to the fact that the requirement for generics - the harmonization of SmPC and PILs - has to be done by their own and it is not done by the originators. Therefore the CADREAC procedure has a clear advantage for generic companies. For originators it may be advisable to use the NP.

Due to the identity of dossier and documentation in EU MSs and CADREAC countries, the handling of the life-cycle management – for example handling of any changes and VARs – is clearer and easier because VARs can be handled identical to EU for MPs authorized via CADREAC procedure. The documentation for the VAR has to be identical to the documentation submitted (and approved) in EU. VARs have to be submitted in the CADREAC countries in parallel to the submission in the RMS or after the approval of the VAR in the RMS. Normally, it is easier to submit VAR after the approval in the RMS because the CADREAC countries will wait for the approval in the RMS and the availability of the approval letter of the VAR in EU and the VAR AR of EU before the CADREAC DRAs grant the VAR.

However, the applicant has the obligation to handle the life-cycle management (e.g. handling of any changes (VARs) and RENs (because of identity of dossier and labeling)) identical to EU if the product was authorized via simplified CADREAC procedure. There is no flexibility and choice!

Whereas if the product was authorized via NP, there is no obligation to handle the life-cycle management identical to EU which gives some flexibility to the applicant.

Another point which should be considered is the fact that the evaluation of the dossier is easier and faster (for the authorities) if using the simplified CADREAC procedure because a complete evaluation of the dossier has not to be done by their own. To support this evaluation, documents like EU AR and consolidated list of questions and answers are requested.

Therefore, less or no questions/objections are raised by CADREAC authorities if applicant uses the simplified CADREAC procedure compared to the NP. If a complete evaluation is done (if applicant applies via NP), normally more questions/objections are raised by authorities because no pre-evaluation data like EU AR are made available. From this point of view, the CADREAC procedure is definitely the faster procedure because the time for evaluation will be certainly shorter due to the availability of documents like EU AR and consolidated list of questions and answers compared to NP.

On the other hand, the fact that no complete evaluation of the dossier is done by DRAs in CADREAC countries - because documents like EU AR and consolidated list of questions and answers are available – can also be a disadvantage especially for products for which difficulties occur during MRP like a lot of questions raised by CMS, restriction of indications, expansion of adverse effects or withdrawals of countries from the procedure.

After 9 of 12 CADREAC countries joined the EU, it was (and will be) possible to include nationally authorized products (via simplified CADREAC procedure or via NP) in an existing MRP (90 day procedure) by the mean of a repeat use MRP, but there was (and will be) no legal obligation to do so.
For inclusion, a so called „administrative MRP“ (30 day procedure) was (and still is) possible for products which were authorized in the CADREAC countries via simplified procedure to include CADREAC countries into the MRPs because of the identity of documentation and labeling. This may also be an advantage to use the simplified CADREAC procedure for national applications, especially with regard to Romania as a candidate country for the EU.

One limitation factor for the recommendation which procedure (simplified CADREAC procedure or NP) should be used is the fact that simplified CADREAC procedures are not applicable for all products and MAAs. Simplified CADREAC procedures can only be used for products which were authorized in EU via CP or MRP. This means especially for older products which were authorized in EU via NP (before 1995), simplified CADREAC procedures are not possible. For these products the applicant has no choice between the two procedures; he has to apply via NP.

Another important aspect which should considered is the fact that the simplified CADREAC procedure offers two different variants to apply for a MA as described earlier (please refer to Section 2.2 *„Description of the CADREAC procedure“*).
The main difference between variant I and II is the timing for submission of the application in the C-CMS. Whereas variant I can only be used after finalization of the MRP in EU (submission any time after completion of the respective MRP, before or when updated AR is available), the variant II can also be used after the RMS has issued the AR which means in parallel with the MRP in EU.
Variant II was only possible in Slovakia but presubmission consultation was required. In all current CADREAC MSs including Romania only variant I is possible.
This means that the applicant has to wait until the finalization of the MRP in EU and the availability of the updated AR before he can apply for MA in CADREAC countries via simplified CADREAC procedure.
This may be a time disadvantage in favor of the NP for cases where the start of the MRP is delayed or an updated AR is available with delay, only.

On the other hand, this variant has the advantage that the documentation and labeling documents approved by EU RMS and CMSs through MRP are used for applying the MA in the CADREAC countries and the availability of the updated AR and the consolidated list of questions and answers. When using variant I the risk is very low to be required by the authority to make changes in the documentation or labeling documents as the documentation submitted is MRP-approved.

As mentioned before, variant II can be used after the RMS has issued the AR which means in parallel with the MRP in EU. This means that the approval of the MAA in the CADREAC countries will be received earlier than for variant I because variant II is running parallel to the MRP.

On the other hand, for variant II it is necessary that the applicant will inform the CADREAC DRA on each step of the relevant MRP and also on the changes in the SmPC during the MRP. The applicant should also provide - at the end of the MRP - the final SmPC to the CADREAC countries.

This means that the workload for the applicant is higher than using variant I. Also the risk of requests of the CADREAC authorities to make changes in the documentation or labeling documents is higher than for variant I but smaller than in the national Romanian MA procedure. Until today, in Romania variant II cannot be used.

The date when the applicant can apply for a MA in the CADREAC countries is an important factor for the decision which procedure will be used.

The prerequisite to start the registration procedure in a CADREAC country is the availability of a CPP from at least one EU MS.

A CPP establishes the status of the pharmaceutical product and the status of the applicant for the certificate in the exporting country. The CPP would be requested by the exporting company and the local authority would be applying for the certificates. The country in which the product is manufactured would be applied for the certificate. The CPP is generally for one single product. If one product is available in different strengths and dosage forms, a separate CPP has to be ordered for each strength and dosage form, also if it is produced by the same manufacturer. Generally, the authority which granted the MA is also responsible to issue the CPP. For each product for which a CPP should be requested the following information has to be provided (according to the explanatory notes issued by WHO):

- Exporting (certifying country)
- Importing (requesting country)

- Name and dosage form of the product
- Active ingredient(s) and amount(s) per unit dose
- Information on whether the licensed product is to be placed on the market for use in the exporting country (Marketing Status)
- European Public Assessment Report (EPAR)
- Approved product information (SmPC)
- Information on whether this product is actually on the market in the exporting country
- Number of product licence and date of issue
- Product licence holder (name and address)
- Applicant for certificate, if different from licence holder (name and address)
- Applicant for certificate (name and address)
- Status of applicant
- Does the certifying authority arrange periodic inspections of the manufacturing plant in which the dosage form is produced?
- Periodicity of routine inspections (years)
- Has the manufacturing process of this type of dosage form been inspected?
- Do the facilities and operations conform to GMP as recommended by the WHO?

The CPP provides for each MP important regulatory information of the pharmaceutical product. The CPP gives also information about the GMP status of the pharmaceutical company. This information about GMP is for some countries very important and it is also very important that CPP provides the GMP status because some German authorities do not provide companies with special GMP certificates.
In some countries the CPP is acknowledged as proof for safety and efficacy of a pharmaceutical product.
Therefore the approval of the product in one EU MS (e.g. in the RMS) is a prerequisite to start the registration procedure in the CADREAC countries, this is true for both procedures, for the CADREAC procedure as well as for the NP.

It is possible to apply for a MA via NP as soon as the MP is authorized in one EU MS (e.g. in the RMS) because of the availability of the CPP. The applicant has not to wait until the RMS has issued the AR.
Therefore, the NP offers the earliest possibility to apply for a MA in the CADREAC countries.

The earliest date to apply for a MA in the CADREAC countries via simplified CADREAC procedure offers variant II (submission after the RMS has issued the AR which means in parallel with the MRP in EU) of the simplified CADREAC procedure.
Whereas variant I can only be used after finalization of the MRP in EU (submission any time after completion of the respective MRP, when updated AR is available); therefore this is the possibility which offers the latest date to apply for a MA.
This means, the CADREAC procedure can always be started later than the NP.

The costs of the procedures are also one issue which should be taken into consideration. Normally the simplified CADREAC procedure is more expensive than the NP. In Romania, the simplified CADREAC procedure costs approx. 1.500 USD whereas NP costs 973 USD (approx. 35% cost savings).

Another point which should be considered is the requested dossier format. For the CADREAC procedure the original MRP dossier have to be used. Normally the MRP dossiers are either in NtA-format or in CTD-format, but it may happen that also mixed dossiers were submitted to the EU CMSs for MRPs based on an earlier existing national authorization in RMS (e.g. Part III and IV/Module 4 and 5 in the old NtA-format and Part I and II/Module 2 and 3 in CTD-format). Whereas for the NP the complete MAA dossier has to be presented either in NtA or in CTD format, mixed and/or hybrid dossiers are not acceptable. This leads to an additional workload at the companies because for many dossiers neither complete CTD nor complete old NtA dossiers are available at the moment. Therefore the CADREAC procedure seems to be more comfortable for the companies from this point of view.

Maybe, the most important point in evaluating both procedures is relating to the flexibility of the applicant/MAH.
It can be a disadvantage if the applicant uses the simplified CADREAC procedure because he is not flexible regarding the documentation because of the commitment to handle the dossier and labeling documents equivalent/identical to EU by submitting the requested documentation and declarations.
The applicant has more flexibility by using the NP because the dossier and labeling documents do not mandatory have to be identical to dossier and labeling documents submitted and approved in EU. It is for example possible to apply in CADREAC countries for more

and/or other indications as approved in EU. If using the simplified CADREAC procedure the applicant can only apply for the same indications as approved in EU.

It should also be taken into account that most of the authorities in the CADREAC countries prefer the simplified CADREAC procedures for products authorized in the EU via CP or MRP instead of using the NPs.

In some of the Ex-CADREAC countries (new EU MSs) it was mandatory since 2003 to use the simplified CADREAC procedures for products authorized in the EU via CP or MRP, instead of using the NP. These authorities did not accept any longer MAAs via NP for products authorized in the EU via CP or MRP because the CADREAC procedures take less time than NPs. For the new EU MSs the CADREAC procedure offers the possibility adn advantage to register a lot of MPs within a few months and the MA procedures could be finalized before the EU accession date. At the day of accession (1st May 2004), art. 17(2) & 18 of Directive 2001/83/EC applied to all pending applications :

- Irrespective of the date of submission
- No transition period
- Applicable only if same medicinal product is under evaluation in the CADREAC MSs as approved in EU (same qualitative and quantitative active ingredients and same pharmaceutical form)
- Except for line extensions and well established use applications

„Art. 17

1. MSs shall take all appropriate measures to ensure that the procedure for granting an authorization to place a MP on the market is completed within 210 days of the submission of a valid application.

2. Where a MS notes that an application for authorization is already under active examination in another MS in respect of that MP, the MS concerned may decide to suspend the detailed examination of the application in order to await the AR prepared by the other MS in accordance with Art. 21(4).

The MS concerned shall inform the other MS and the applicant of its decision to suspend detailed examination of the application in question. As soon as it has completed the examination of the application and reached a decision, the other MS shall forward a copy of its AR to the MS concerned.

Art. 18

Where a MS is informed in accordance with Art. 8(3)(l) that another MS has authorized a MP which is the subject of an application for authorization in the MS concerned, that MS shall forthwith request the authorities of the MS which has granted the authorization to forward to it the AR referred to in Art. 21(4). Within 90 days of the receipt of the AR, the MS concerned shall either recognize the decision of the first MS and the SmPC as approved by it or, if it considers that there are grounds for supposing that the authorization of the MP concerned may present a risk to public health, it shall apply the procedures set out in Articles 29 to 34.“

All pending MAAs which were not granted on 1st May 2004 were rejected and had to be submitted again according to the current EU legislation (via MRP or CP) (cf. 7.1, 7.2, 7.7, 7.8).

In some other countries (like Romania) it is still possible to apply for products authorized in EU via MRP or CP via NP.

For products authorized in EU via NP the applicant has to apply also in the CADREAC countries via NP, e.g. for products authorized before 1995 (as MRP becomes mandatory).

V. CONCLUSION AND OUTLOOK

5.1 Recommendation which procedure to use for which product

In general, different regulations and procedures regarding the application for a new MA exist in Romania. The main goal of these is to protect human health by following them and to describe in detail on how to approve new safe MPs. Each MP has to show highest quality, safety and efficacy.

The extent and the level of the requirements depend on the potential risk of harmful effects on human beings, animals and environment.

There are several regulatory aspects which have to be taken into account to decide which procedure – simplified CADREAC procedure or NP – should be used to apply for a MA in the Romania (and also in the other CADREAC countries).

The two CADREAC procedure for products authorized in EU via MRP offers a good possibility to register a MP, which was authorized in EU via MRP, in the CADREAC countries with the respective simplified procedure. The basis for the assessment for the CADREAC DRAs is the original dossier, which was submitted and approved in EU for MRP by EU MSs (RMS and CMSs).

The NP within this thesis described in detail for Romania is a complete independent procedure, where a country specific dossier is submitted. The complete evaluation of the dossier is also done independently by the national authority (NMA). Both procedures – CADREAC procedure for products authorized in EU via MRP and NP – bear different advantages and disadvantages as discussed in sections 2.4, 3.3 and 4, as for example the following:

The CADREAC procedure offers the possibility of harmonization of labeling texts (SmPC and PIL) and the documentation of MP authorized in the EU MSs via MRP with the CADREAC MSs due to the fact that the documentation and labeling documents which have to be submitted are identical to those approved in EU. In this case one identical dossier and identical labeling documents are approved in EU MSs and CADREAC countries. This is an advantage, because also life-cycle management (e.g. handling of any changes and VARs) can be handled very simple because of identity of dossiers and labeling documents with EU.

On the other hand, this harmonization of labeling documents (SmPC and PIL) is a prerequisite for generics, but is done by the originators. Thus, generics can apply for, can get easier MAs, and can come earlier and easier to the market which is a clear advantage for generics and a big disadvantage for originators. If the product is authorized via NP in each CADREAC

country the labeling documents (SmPC and PIL) are normally not harmonized. In this case, the way for generics to get MAs is more complicated due to the fact that the requirement for generics - the harmonization of SmPC and PILs - has to be done by their own and it is not done by the originators. Therefore the CADREAC procedure has a clear advantage for generic companies.

Another advantage of the simplified CADREAC procedure is the benefit of time because this procedure takes less time than the NP for getting the respective MA. CADREAC procedure takes between 4 and 12 months depending on the review time in each country (shortest country is Bulgaria with 120 days, Romania needs 6 months (usually there is a delay of 3 to 4 months) and the longest country was Hungary with 12 months).

After evaluating all advantages and disadvantages of both procedures it seems adequate to recommend the usage of the simplified CADREAC procedure for products authorized in EU via MRP for all new products which have proven quality, safety and efficacy and for which a documentation of high quality is available.

The simplified CADREAC procedure can also be used for all products authorized in EU via MRP for products where the European procedure (MRP) was without major difficulties; major difficulties mean discussion about the efficacy and safety of the product, restriction of applied indications or increase of adverse reactions and withdrawal of countries from the procedure.

In case of one or more of these difficulties during the European procedure (MRP), the NP should be used for applying for a MA in the CADREAC countries to avoid further questions and difficulties. If for such products the simplified CADREAC procedure is used it may happen that the authority does not approve the product and rejects the MAA.

Of course, the recommendation of the usage of the simplified CADREAC procedure for products authorized in EU via MRP is also true for the CADREAC procedure for products authorized in EU via CP (cf. 7.4, 7.5).

For products, which were authorized in EU via NP, there is no choice. The NP has to be used for applying for a MA in the CADREAC countries, because the simplified CADREAC procedure cannot be used.

The NP should also be used if the applicant/MAH wants to apply at the earliest date for a MA because the NP can be used earlier than the simplified CADREAC procedure. The NP can be used as soon as the product is approved in one EU MS, there is no obligation to wait for the start of the MRP.

If the applicant/MAH wants to keep the registration more flexible, the NP should be used. Using the NP means that the dossier and labeling documents do not mandatory have to be identical to dossier and labeling documents submitted and approved in EU. This also bears opportunity to apply in CADREAC countries for more and/or other indications as approved in EU. If using the simplified CADREAC procedure the applicant can only apply for the same indications as approved.

To sum up, aspects like flexibility of the applicant/MAH, duration of the MA procedure, evaluation procedure of the dossier, date for submission of MAA, lifecycle of a product, harmonization of dossier and labeling documents (SmPC and PIL), costs of the procedure and of course the product itself should be considered for the decision which procedure to be used for the MAA of a certain product in the CADREAC countries.
Both procedures – national and CADREAC procedure – have the identical main goal which means to protect human health and to make available new MPs as soon as possible.
To evaluate the quality, safety and efficacy of the MPs is mandatory for getting approvals of the MPs.

5.2 Outlook on the future of the CADREAC procedures

5.2.1 Future activities in CADREAC

As mentioned before at the moment there are three CADREAC members left i.e. Bulgaria, Romania and Turkey. Bulgaria and Romania will join the EU in 2007, whereas for Turkey no date for accession is confirmed. Therefore the CADREAC procedure will exist at least until 2007 - the EU accession date for Romania and Bulgaria. When these two countries have joined the EU (2007) it seems that the CADREAC procedure will not be necessary and will not exist any longer, except new countries will join as members to CADREAC - like Belarus, Bosnia-Herzegovina, Croatia, Republic of Moldova, Macedonia, Serbia and Montenegro, Switzerland, Ukraine, etc.

In this circumstance, in October 2004, EFPIA representatives paid a visit to Croatia for two days to negotiate with Croatian Drug Agency to speed up approval process and to harmonize legislation with CADREAC procedures. Topics discussed during this meeting were CP, MRP and DP, Phasing In, CADREAC, the Agency Income and Data protection (cf. 7.16 and cf. 7.17).

In November 2004, Croatia signed the CADREAC agreement the first time with Romania (the CADREAC secretariat), but agreement was not valid at that time because there were only 3 signatures (Croatia, Bulgaria and Romania) obtained and 6 signatures were required. Therefore it took until beginning of April 2005 collecting all 6 signatures for Croatia. The main problem was that there were not enough CADREAC countries left after EU accession of nine of them to sign the CADREAC agreement for new assessing countries, therefore it was agreed that countries from old CADREAC (new EU MSs) can sign agreement, too. The 6 signatory countries for the agreement were Croatia, Hungary, Bulgaria, Slovakia, Romania and Czech Republic. The CADREAC agreement for Croatia came into force on 1st May 2005. It shows that CADREAC is acquiring new countries as their members to ensure that CADREAC will exist also in the future.

5.2.2 New EU legislation (EU Review 2004)

Another point, which should be taken into consideration, is the new pharmaceutical legislation in EU (so called "EU Review 2004"), which has also an important impact on the future of the CADREAC procedures.

5.2.2.1 Changes in the centralized procedure (CP)

The CP, which is described in the Council Regulation 2309/93 (cf. 7.7), came into operation on the 1st January 1995. The legal basis was defined further in 1998 by Commission communication 98/C 229/03 (cf. 7.18) (also released as C98/2016 (cf. 7.19)), which clarified aspects relating to the scope of the procedure, naming of MPs and parallel distribution of centrally, authorized MPs.

The Council Regulation 2309/93 (cf. 7.7) also established the EMEA (also called "Agency") and the CPMP, the scientific committee - which is responsible for the evaluation of new MAAs for MPs for human use - under the direction of the Agency.

The Regulation 2309/93 (cf. 7.7) and especially the CP were built on the experience of the concertation procedure, which had been set up under Council Directive 87/22/EEC (cf. 7.20).

Apart from the role of the EMEA one of the key differences of the CP - compared with the previous concertation procedure - is that the CPMP decision leads to a binding Commission decision. The positive Commission decision results in the approval of a single Community MA throughout the EU. The results of the scientific evaluations of the dossier are made available to the public in the form of EPARs (which are available on the EMEA website).

The MAAs are submitted directly to the EMEA which forward the MAAs - after they passed the validation phase - to the scientific committee, the CPMP for the scientific evaluation. This scientific evaluation is done within 210 days by the CPMP. The CPMP extracts out assessment work to experts in one of the MSs (the "Rapporteur"). After the conclusion of the scientific evaluation the CPMP opinion is transmitted to the EC to be transformed into a single Community MA applying throughout the EU.

Under Regulation 2309/93 (cf. 7.7) the CP is compulsory for MPs derived from biotechnology and optional for other innovative new MPs.

Due to the EU review 2004, the new council Regulation 726/2004 (cf. 7.8) which was adopted at 31st March 2004 and came into force on the 20th May 2004 (Art. 90 of 726/2004 *"shall enter into force on the twentieth day following that of its publication in the Official Journal of the EU" (cf. 7.8))* will, after full implementation, replace Regulation 2309/93 (cf. 7.7).

In the new regulation, the role of the Agency was strengthened and its name was changed from *"The European Agency for the Evaluation of MPs"* to *"The European Medicines Agency"*; but the abbreviation EMEA remains. The name of the *"Committee for Proprietary MPs"* (CPMP) was changed at that time to *"The Committee for MPs for Human Use"* (CHMP).

Other parts of the regulation are not yet implemented but have to be implemented until 20th November 2005 (Art. 90 of 726/2004 *"By way of derogation from the first paragraph, Titles I, II, III and V shall apply from 20 November 2005 and point 3, fifth and sixth indent of the Annex shall apply from 20 May 2008" (cf. 7.8)).*

After the full implementation of the revised Community legislation in November 2005 several changes will be made with regard to the CP. These include an expansion of the scope of the procedure, establishment of a procedure for conditional MAs, formalization of an accelerated procedure and management of compassionate use programmes. In addition, assistance will be available for small and medium-sized enterprises.

The new regulation states that the CP will be mandatory for certain MPs:

- It continues to be compulsory for biotechnological products
- From 20th November 2005 the CP will also be mandatory for MPs that contain a new active substance and which will be used for the treatment of AIDS, Cancer, neurodegenerative disorders, Diabetes and with effect from 20th May 2008 also for the treatment of auto-immune diseases and other immune dysfunctions and viral diseases. The definition for a new active substance in this context means that the

active substance concerned was not authorized in the EU at the date of coming into force of the regulation

For the CADREAC countries and their CADREAC procedure for products authorized in EU via CP there are no direct influences on this CADREAC procedure itself due to the change of the EU legislation.
But in future, there will be more CPs in EU leading to more CADREAC procedures for products authorized via CP.
According to the current CADREAC procedure for products authorized in EU via CP, the MAAs for simplified CADREAC procedure may be submitted both before and after the final Commission Decision has been issued depending on the requirements of the CADREAC DRA concerned (cf. 7.4 and cf. 7.5). Practically, each CADREAC DRA allows the start of the simplified CADREAC procedure first after issuing the Commission Decision in EU.
For these increased number of CADREAC procedures it is advisable to apply for a MA in the CADREAC countries also before the Commission Decision in EU is issued by using the simplified CADREAC procedure for products authorized in EU via CP. Therefore the CADREAC DRAs should change their requirements accordingly.

5.2.2.2 Changes in the mutual recognition (MRP) and establishment of the decentralized procedure (DP)

Council Directive 93/39/EEC (cf. 7.21) which amended Council Directive 75/319/EEC (cf. 7.22) established the MRP. The MRP came into force on 1st January 1995. The provisions of Directive 75/319/EEC have since been incorporated into the Codification Directive 2001/83/EC (cf. 7.1). In 1998 the legal basis was further defined by Commission communication 98/C 229/03 (cf. 7.18) (also released as C98/2016 (cf. 7.19)).
The Directive 2001/83 (cf. 7.1) - the codification directive - is amended by Directive 2004/27 (cf. 7.2) and 2004/24 (for herbal drugs) (cf. 7.15). The two Directives 2004/27 and 2004/24 were adopted on 31st March 2004 and have to be implemented into national law: *"MSs shall bring into force the laws, Regulations and administrative provisions necessary to comply with this Directive no later than 30 October 2005. They shall immediately inform the Commission thereof. When MSs adopt these measures, they shall contain a reference to this Directive or shall be accompanied by such a reference on the occasion of their official publication. The methods of making such reference shall be laid down by the MSs."*
Therefore a transition period of 18 months is foreseen. This means that the Directives have to be implemented into national law of the EU MSs until November 2005.

It remains open if the CADREAC procedure for products authorized in EU via MRP will be adapted to the EU review 2004, because after the review has been implemented (November 2005) there will exist a DP and a MRP in EU.
The review contains the dividing of the MRP into two procedures, the MRP for a MP already authorized in at least one EU MS, and the DP for a MP not authorized within the EU yet.
The DP - a new procedure to apply for a MA in the EU - will come into force in November 2005. It will be applicable in cases where a MA in more than one MS shall be obtained and an authorization within the EU does not yet exist. The DP as well as the MRP can only be chosen in cases where the CP is not mandatory.
The legal basis for the DP lies down in Art. 28.3-4 of Directive 2001/83 (cf. 7.1), as amended by 2004/27 (cf. 7.2): *"In cases where the MP has not received a MA at the time of application, the applicant shall request the RMS to prepare a draft AR, a draft SmPC and a draft of the labelling and PIL. The RMS shall prepare these draft documents within 120 days after receipt of a valid application and shall send them to the concerned MSs and to the applicant. Within 90 days of receipt of the documents (…) the MSs concerned shall approve the AR, the SmPC and the labelling and PIL and shall inform the RMS accordingly. The RMS shall record the agreement of all parties, close the procedure and inform the applicant accordingly."*

The principle of the DP is the involvement of the CMSs in an earlier stage of the procedure compared to the MRP. Therefore, identical dossiers shall be submitted simultaneously to all EU MSs where a MA should be granted. The RMS - chosen by the applicant/MAH - is obliged to prepare a draft AR within 120 days and send it to the CMSs. The CMSs shall then either approve the assessment of the RMS within a period of 90 days or the MAA will continue with the arbitration procedures.
Finally, all MS involved in the DP shall simultaneously reach the same decision – granting of a MAA or rejection of a MAA - based on harmonized information for the MP.
This shall minimize disagreements and facilitate the MAAs in as many markets as possible.
After the implementation of the directive 2004/27 (cf. 7.2) and 2004/24 (cf. 7.15) (November 2005), it can be expected that the number of MRPs will be reduced, whereas the number of DPs will increase, because the condition for a MRP is that one national MA exists in the EU that can act as RMS. If no national MA exists in the EU and the applicant wants to apply for more than one MA, the DP has to be used. This means, that after November 2005 the MRP may be interesting especially for small and medium-sized or local working companies which

would like to apply for only one MA in EU via NP first. Any time after the positive finalization of this procedure (granting of the MA in one EU MS), it is possible for these companies to apply for more MAs in EU by using the MRP.

For the CADREAC procedure for products authorized in EU via MRP, it is necessary that an adaptation to the EU procedures (DP and MRP) has to be performed. To be in accordance with the EU legislation, there should already be CAREAC procedures established that can be used for both European procedures - DP and MRP. Therefore, the change of the EU legislation with regard to MRPs and DPs has a major influence on the CADREAC countries and their procedures. So far there exists only a CADREAC procedure for products authorized via MRP and there is no CADREAC procedure established which could be used for products authorized in EU via DP. A new CADREAC procedure for product authorized in EU via DP has to be created.

It remains open if the CADREAC procedure will be adapted to the new EU legislation.

VI. SUMMARY

The **C**ollaboration **A**greement of **D**rug **R**egulatory Authorities in **E**uropean **U**nion **A**ssociated **C**ountries (CADREAC) was a collaboration of 12 countries, which started in 1997. The Heads of Drug Regulatory Authorities (DRAs) in the European Union (EU) associated countries agreed to sign the CADREAC agreement in order to start a formal collaboration during the first meeting of DRAs in Central and Eastern Europe Countries (CEECs), 12 to 14 June 1997 in Sofia.

Originally, the members of CADREAC were Bulgaria, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, Slovenia and Turkey. Nine of these countries joined the EU on 1st May 2004, therefore in April 2005 there were only three CADREAC countries left – Bulgaria, Romania and Turkey.

The mission of CADREAC is facilitation of smooth transition of regulatory conditions in EU associated countries to achieve regulatory standards required by Acquis Communautaire (compliance to article (Art.) 6 of Directive 2001/83/EEC (cf. 7.1) amended by Directive 2004/27 (cf. 7.2): *"No medicinal product (MP) may be placed on the market of a Member State (MS) unless a marketing authorization (MA) has been issued by the competent authorities (CAs) of that MS in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 2309/93. The authorization referred to in paragraph 1 shall also be required for radionuclide generators, radionuclide kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals."*), which are:

- Implementation of EU regulatory standards
- Involvement in professional activities within EU
- Introduction of mutually recognition procedures (MRP)
- Introduction of centralized procedures (CP)
- Development of common strategies
- Preparation of meetings
- Information exchange

A CADREAC Standard Operating Procedure (SOP), CADREAC SOP-3 (2001) was adopted in April 2001, defining the responsibilities and function of a CADREAC secretariat (cf. 7.3). The secretariat of CADREAC is located in Romania since March 2004.

In addition to the CADREAC MSs, the following countries have the status of observers: Belarus, Bosnia-Herzegovina, Croatia, Republic of Moldova, Switzerland and Serbia and Montenegro.

The CADREAC countries developed certain guidelines and procedures as a preparation for their EU-accession, e.g. the so-called simplified CADREAC procedures:

- Common procedure on the granting of MAs by CADREAC DRAs for MPs authorized in the EU by CP - in force since January 1999
- Common procedure on the granting of MAs by CADREAC DRAs for MPs authorized in the EU by MRP - in force since May 2001 (The 1st revision of the guideline - published on 10th June 2001 - includes the retrospective inclusion of MPs for human use authorized in EU via MRP in the Common CADREAC Simplified System)
- Common CADREAC Procedure (CCP) for retrospective inclusion of centrally authorized MPs for human use in the Common CADREAC Simplified System - in force since May 2001

The first two different CADREAC procedures - the CADREAC procedure for products authorized in EU via CP and the CADREAC procedure for products authorized in EU via MRP - offer a good possibility to register a MP, which was authorized in EU via MRP or CP, in the CADREAC countries with the respective simplified procedure. The basis for the assessment for the CADREAC DRAs is the original dossier, which was submitted and approved in EU for MRP by EU MSs (Reference Member State (RMS) and Concerned Member States (CMSs)) or for CP by European Commission (EC).

The national procedure (NP) within this thesis described in detail for Romania is a complete independent procedure, where a country specific dossier is submitted. The complete evaluation of the dossier is also done independently by the national authority (National Medicines Agency (NMA) in Romania). Both procedures – CADREAC procedure for products authorized in EU via MRP and NP – bear different advantages and disadvantages, as for example the following:

The CADREAC procedures offer the possibility of harmonization of labeling texts (Summary of product characteristics (SmPC) and patient information leaflet (PIL)) and the documentation of MP authorized in the EU MSs via MRP or CP with the CADREAC MSs due to the fact that the documentation and labeling documents which have to be submitted are identical to those approved in EU. In this case one identical dossier and identical labeling documents are approved in EU MSs and CADREAC countries. This is an advantage, because also life-cycle management (e.g. handling of any changes and Variations (VARs)) can be handled very simple because of identity of dossiers and labeling documents with EU.

On the other hand, this harmonization of labeling documents (SmPC and PIL) is a prerequisite for generics, but is done by the originators. Thus, generics can apply for, can get easier MAs, and can come earlier and easier to the market which is a clear advantage for generics and a big disadvantage for originators. If the product is authorized via NP in each CADREAC country the labeling documents (SmPC and PIL) are normally not harmonized. In this case, the way for generics to get MAs is more complicated due to the fact that the requirement for generics - the harmonization of SmPC and PILs - has to be done by their own and is not done by the originators. Therefore the CADREAC procedure has a clear advantage for generic companies.
Another advantage of the simplified CADREAC procedures is the benefit of time because these procedures take less time than the NP for getting the respective MA. The CADREAC procedure for products authorized in EU via MRP takes between 4 and 12 months depending on the review time in each country (shortest country is Bulgaria with 120 days, Romania needs 6 months (usually there is a delay of 3 to 4 months) and the longest country was Hungary with 12 months). The CADREAC procedure for products authorized in EU via CP takes between 2 and 7 months depending on the review time in each country (shortest country was Estonia with 2 months, Romania needs 3 months and the longest country is Turkey with 7 months).

To sum up, aspects like flexibility of the applicant/marketing authorization holder (MAH), duration of the MA procedure, evaluation procedure of the dossier, date for submission of marketing authorization application (MAA), lifecycle of a product, harmonization of dossier and labeling documents (SmPC and PIL) and costs of the procedure should be considered for the decision which procedure to be used for the MAA of a certain product in the CADREAC countries.

The future of the CADREAC procedure is influenced by the EU-review and further states to join the agreement. Due to the new European procedures – MRP and decentralized procedure (DP) – the CADREAC guideline for a product authorized in EU via MRP will have to be revised. Just recently, Croatia joined the CADREAC agreement.

VII. REFERENCES

7.1 Directive 2001/83/EECof the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

7.2 Directive 2004/27 EEC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use

7.3 CADREAC SOP-3: Responsibilities and function of CADREAC secretariat

7.4 Procedure on the granting of MAs by CADREAC Drug Regulatory Authorities for medicinal products for human use authorized in the EU following the centralized procedure and the variation and renewal of such marketing authorizations

7.5 Guidance for simplified procedure for MA of medicinal products authorized in the European Union following the Centralized procedure and for variations and renewals to these MAs in CADREAC area

7.6 Common CADREAC Procedure (CCP) for retrospective inclusion of centrally authorized MPs for human use in the Common CADREAC Simplified System - in force since May 2001

7.7 Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products

7.8 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

7.9 Procedure on the granting of MAs by CADREAC Drug Regulatory Authorities for human medicinal products already authorized in EU member states following the decentralized procedure

7.10 DECISION No. 8/04.05.2001 regarding the approval of procedure on the granting of MAs by CADREAC Competent Authorities for medicinal products for human use already authorized in European Union Member States following the decentralized procedure (Romania)

Annex 1: PROCEDURE ON the granting of MAs by CADREAC COMPETENT

Authorities for MEDICINAL PRODUCTS FOR HUMAN USE ALREADY authorized in European Union Member States following the decentralized Procedure

7.11 DECISION No. 1/17.01.2003 regarding the approval of Regulations on MA and surveillance of medicinal products for human use (Romania)

Annex 1: Regulations on MA and surveillance of medicinal products for human use

7.12 MRFG Best practice guide for Mutual Recognition Procedure

7.13 Decision No. 27/2000 regarding the approval of regulations on MA and surveillance of medicinal products for human use and of the Norms on the documentation required for MA or renewal of MA of medicinal products for human use

7.14 DECISION No. 24/15.11.2002 regarding the laboratory control within MA/renewal of MA procedure

7.15 Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use

7.16 Record of Meeting with Croatian Agency for medicinal products and Medical devices Zagreb, 12th October, 2004

7.17 CEEC Regulatory group teleconference on Croatia, 11 August 2004

7.18 Commission communication 98/C 229/03: Commission communication on the Community marketing authorisation procedures for medicinal products

7.19 Commission Communication C98/2016 of 22 July 1998 (OJCE C229 of 22 July 1998)

7.20 Council Directive 87/22/EEC, of 22 December 1986 on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology

7.21 Council Directive 93/39/EEC of 14 June 1993 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products

7.22 Council Directive 75/319/EEC, of 20 May 1975, on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products

VIII. APPENDICES

8.1 Appendix 1: Information Sharing Letter

ANNEX 1

Text in italics should be replaced by the data specific to individual submissions.

Name of the product:

Mutual Recognition Procedure No.:

Approval of Information Sharing between the *National Authority of the Reference Member State* and the *Competent CADREAC Authority*

The *Marketing Authorisation Holder (Drug Master File Holder) in the Reference Member State* hereby notifies to the *National Authority of the Reference Member State* of the submission of an application for the marketing authorisation of the following medicinal product to the *Competent CADREAC Authority*:

name of the medicinal product, dosage form, strength, package size/s
(differences in brand name, if any)
proposed marketing authorisation holder in the country of the CADREAC DRA

The *Marketing Authorisation Holder (Drug Master File Holder) in the Reference Member State* agrees that the *National Authority of the Reference Member State* may make available to the *Competent CADREAC Authority* any information concerning the quality, safety and efficacy of the above product. The extent of this information shall not exceed that which is made available to EU Member States. In the case that variant II of this simplified procedure is used the *Marketing Authorisation Holder (Drug Master File Holder) in the Reference Member State* agrees with the participation of the CADREAC expert in the break out session.

The information will be used by the *Competent CADREAC Authority* in accordance with applicable laws and regulations for the marketing authorisation and safe use of medicinal products in *the country of the CADREAC DRA*.

This Declaration is made as of the date first written below and remains valid for the period during which the product is authorised or registered in the Member States of the EU and *the country* of the *CADREAC DRA* respectively.

Date

Signature of the Marketing Authorisation Holder
(Drug Master File Holder)
First name, family name:
Address:

8.2 Appendix 2: Report on the marketing authorization granted by the CADREAC DRA of the medicinal product subjected to the MRP in the EU

ANNEX 2

Competent CADREAC Authority

***TO:** Competent Authority of the Reference Member State*

REPORT ON THE MARKETING AUTHORISATION GRANTED BY THE CADREAC DRA OF THE MEDICINAL PRODUCT SUBJECTED TO THE DECENTRALISED PROCEDURE IN THE EU

Name of the product in the RMS, pharmaceutical form/s, strength/s relevant to this report

INN or common name of the active ingredient/s

DP number/s of the product

Name of the MA holder in the RMS

Report on acceptance of the DP MA

Report on disagreement with the DP MA*

Report on refusal of variation*

Report on retrospective inclusion of the product in the database of products approved according to this procedure

Request to RMS*

Name of the product in the CADREAC DRA's country concerned

National Marketing authorisation number/s

Date of issue of national marketing authorisation decision

Name of the marketing authorisation holder in the CADREAC DRA's country concerned

Authorised dosage forms, strengths, package sizes in CADREAC DRA's country concerned

Modifications of SPC and PIL (specifying differences, except different name of the product, MA holder, national MA number)

Modifications of labelling (specifying differences, except different name of the product, MA holder, national MA number)

Explanatory notes* :

Enclosures:

Date

Signature of the person responsible
Competent CADREAC Authority

8.3 Appendix 3: Table of specific national requirements of CADREAC DRAs

Adopted: April 2, 2001 **Published: May 3, 2001**

Country	Scope of the procedure	Timing of submission	Expected handling net time	Language of dossier	No. of copies to be submitted	Electronic submission	Need of samples and/or substances	Fees	Date of implementation
Bulgaria	all products submitted for DP in MSs with full dossier and their line extensions (point 3.2 of principles)	variant I	120 days	English Bulgarian	1 copy: all except 3 copies: SPC, PIL and labeling in Bulgarian	encouraged PDF, HTML, XML formats, CD-ROM; along with paper dossier of identical content; SPC, PIL and labelling in Bulgarian submitted on a 3,5 inch floppy diskette, using Word for Windows	1 sample of the medicinal product including packaging	national legislation for MA and for variations	date of publishing
Cyprus	all products submitted for DP in MSs with full dossier and their line extensions	variant I	150 days	English or Greek	1 copy all except 2 copies application form, Part IIE, SPC, Assessment Report, final MRP SPC, proposed Cyprus SPC,PIL and labelling in the Greek language	yes, paper copies of application form, SPC, PIL and packaging material; SPC, labelling and PIL in Greek and English language on a 3.5 floppy diskette or CD. Part III and IV may be submitted in electronic form (CD).	4 samples substances and additional samples upon request	MA 300 Cyp. Pounds plus 10% VAT.	date of publishing
Czech Republic	all products submitted for DP in MSs with full dossier and their line extensions (point 3.2 of principles)	variant I (after day 90 of the DP only)	150 days	English Czech Slovak	1 copy: all except 2 copies: application form, Assessment Report, final MRP SPC, proposed Czech SPC,PIL and labelling	possible submission of the dossier in Pharmbridge-DAMOS, PDF, HTML, XML formats, CD-ROM; together with paper documentation of identical content; SPC, PIL and labelling in Czech shall be on a 3,5 inch floppy diskette, using Word for Windows	1 sample of the medicinal product in the definitive immediate packaging, which need not be definitively labelled (can be submitted subsequently before the MA decision is issued)	MA: 70 000,-CK variation type I - 3 000,-CK (if a decision has to be issued) type II - 30 000,-CK	date of publishing (continuation of the procedure started on March 1, 2000)

Adopted: April 2, 2001 **Published: May 3, 2001**

Estonia	all products submitted for DP in MSs with full dossier and their line extensions	variant I	5 months after receiving the complete documentation	English Estonian	1	encouraged, in addition to paper copy SPC, labelling and PIL in Estonian language on a 3.5 floppy diskette	5 samples substances and additional samples upon request	regular	date of publishing
Hungary	all products authorised by an EU RMS	variant I (after day 90 of the DP only)	12 months net time	English (except SPC and PIL and label text, they must also be in Hungarian) Hungarian	1 copy all except 2 copies: GMP/Product Certificates needed	definitely encouraged in addition to the paper copy. DAMOS/ Pharmbridge, hyperlinked PDF, HTML, XML formats; SPC and PIL (also) in Word	analytical sample (for 5 analysis); samples of the active substance(s) and special reference standards (if applicable) – together with the application final sample of the medicine in its final package – from the first commercial delivery	regular	15 April, 2001
Latvia	all products submitted for DP in MSs with full dossier and their line extensions (point 3.2 of principles)	variant I (after day 90 of the DP only)	national legislation	English German Latvian	1 copy: all except 2 copies : Updated Assessment Report, final DP SPC 2 copies : application form, proposed Latvian SPC, Instruction for Use (PIL) and labelling	encouraged submission of the electronic dossier (on 3,5 floppy diskette, MD Word); SPC and PIL in the Latvian language on a 3.5 floppy diskette (MS Word) (final approved version only)	1 sample of the medicinal product in the definitive immediate packaging, which need not be definitively labelled (can be submitted sub-sequently before the MA decision is issued); adequate quantity of samples and standard substances with the certificate of analysis for three complete analyses	first preparation 1400$, every additional dosage form 700$	in accordance with *Regulations of the marketing authorization of medicinal products* No.381 issued by Cabinet of Ministers October 31, 2000 – starting from January 1, 2003

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Lithuania	all products (point 3.3 of principles). When article 4.8.a) of the Dir.65/65/EEC is applicable – presubmission consultation necessary	variant I	4 – 6 months	English Lithuanian (labelling in Lithuanian: labelling in English acceptable in exceptional cases)	1 copy: all except 3 copies of proposed Lithuanian SPC, PIL)	possible submission of the dossier in Pharmbridge - DAMOS format, CD-ROM (together with paper documentation of identical content); SPC, PIL in English and Lithuanian shall be on a 3,5 inch floppy diskette (in Word for Windows)	1 sample of the medicinal product; adequate quantity of samples and standard substances with the certificate of analysis necessary for three complete analyses upon request	MA: -first preparation NAS 6 000 LTL, known act.subst. 3600 LTL -additional dosage form, different strength -2 400 LTL -variations type I- no fee, however if change in the content of the registration certificate is needed - 400 LTL type II- 1200 LTL	September 1, 2001
Poland	all products submitted for DP in MSs with full dossier and their line extensions	variant I	according to the local procedure 210 days	Polish English	2 copies: all	possible submission of the dossier in Pharmbridge-DAMOS format, CD-ROM; together with paper documentation of identical content; SmPC, PIL and labelling in Polish should be on a 3,5 inch floppy disc, Microsoft Word 2000.	samples of the medicinal product necessary for the analysis samples of active substance reference substances (if referred to in the testing procedures)	NCE: 30 000 PLN Generic: 16 000 variations: type I: 1000 type II: 3000	date of publishing

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Romania	only products submitted for DP in MSs with full dossier and submitted for the simplified procedure to the NMA also with full dossier and subsequently for their line extensions (point 3.1 of principles)	variant I	6 months	English Romanian	1 copy: all except 2 copies: Updated Assessment Report, final MRP SPC, proposed Romanian SPC, PIL and labelling	possible submission of the dossier in Pharmbridge-DAMOS format, DC-ROM, together with paper documentation of identical content; SPC and PIL (final approved version) in the Romanian language on a 3,5 inch floppy diskette using Word for Windows	2 samples of the medicinal product presented in the outer packaging; reference substance (if referred to in the testing procedure)	MA: 1 500 USD variations: -type I simple: 51 USD -type I complex: 100 USD -type II: 141 USD	date of publishing
Slovak Republic	all products, for applications under § 21(5) Act No. 140/1998 Coll. */article 4.8.a) Dir. 65/65/EEC* / - presubmission consultation necessary (point 3.3 of principles)	variant I variant II, but-presubmission consultation required	variant I 5 months, variant II: 90 days for SIDC final opinion, the same timetable as agreed for MRP	English Slovak Czech	1 copy: all except 2 copies : (Updated) Assessment Report 4 copies : application form, proposed Slovak SPC,PIL and labelling, final MRP SPC	encouraged submission of the electronic dossier; SPC and PIL in the Slovak language on a 3.5 floppy diskette using Word for Windows (final approved version only)	1 sample of the medicinal product in the definitive immediate packaging, which need not be definitively labelled (can be submitted subsequently before the MA decision is issued); adequate quantity of samples and standard substances with the certificate of analysis necessary for three complete analyses upon request	MA 75 000.-SK variation 20 000.-SK	date of publishing (continuation of the procedure started on April 10, 2000)
Slovenia	all products submitted for DP in MSs with full dossier and their line-extensions (point 3.2.of principles)	variant I	210 days	Slovenian English	1 copy: all except: 2 copies of the Part II of the file 5 copies of proposed Slovenian PIL & SmPC	SmPC and PIL in the Slovenian language on a 3.5 floppy diskette using Word for Windows (final version only)	adequate quantity of samples necessary for 2. complete analyses	MA: 320000 SIT Var.Type I: 50000 SIT Var.Type II: 150000 SIT line ext.: 200000 SIT	implemented

8.4 Appendix 4: Table of special National Medicines Agency requirements for CADREAC procedure for products authorized in EU via MRP

Country	**Scope of the procedure**	**Timing of submission**	**Expected** handling **net time for finalizing the procedure**	**Language of dossier**	**No. of copies to be submitted**	**Electronic submission**	**Need of samples and/or substances**	**Other specified aspects**	**Date of implementation of the procedure**
Romania	Only for MPs submitted for MRP in EU-MS with full dossier (new chemical entities) and submitted for the simplified procedure to the NMA also with full dossier and subsequently for their line extensions (point 3.1 of principles)	Variant I	6 months	English / Romanian	1 copy: all documentation 2 copies: Updated AR of the reference state, final MRP SmPC, proposed Romanian SmPC, package leaflet and labeling	Possible submission of the dossier in Pharmbridge-DAMOS format, CD-ROM, together with paper documentation of identical content; SmPC and package leaflet (final approved version) in the Romanian language on a 3,5 inch floppy disk using Word format	*2 samples of the MP presented in the outer packaging; *reference substance (if referred to in the testing procedure)		Date of publishing of CCP

8.5 Appendix 5: Contact points for regulatory information exchange – CADREAC

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ANNEX 4

Contact points for regulatory information exchange – CADREAC				
CADREAC DRA	**Name and address**	**E-mail / website**	**Telephone number**	**Fax number**
Bulgaria	Emilia Apostolova National Drug Institute 26 Yanko Sakazov blvd, 1504 Sofia	apostolova@bda.bg http://www.bda.bg	+359-2-9434046	+359-2-9434487
Cyprus	George Antoniou Pharmaceutical Services, Ministry of Health 1475 Lefkosia	rocphc2@cytanet.com.cy	+357-2-309601	+357-2-305802
Czech Republic	Zuzana Rothova State Institute for Drug Control Srobarova 48, 100 41 Praha 10	rothova@sukl.cz http://www.sukl.cz/	+420-2-72185831	+420-2-71732377
Estonia	Kristin Raudsepp State Agency of Medicines Ravila 19 Tartu 50411	kristin@sam.ee http://www.sam.ee/	+372-7-374140	+372-7-374142
Hungary	Ms Sarolta Entz National Institute of Pharmacy Zrinyi u.3, P.O.B 450, Budapest V. H-1372	e-mail: elo@ogyi.hu http://www.ogyi.hu	+36-1-317-4044	+36-1-317-1462
Latvia	Janis Ozolins Inta Kurakina State Agency of Medicines 15 Jersikas Str., Riga LV1003	janis_ozolins@vza.gov.lv inta_kurakina@vza.gov.lv http://www.vza.gov.lv	+371-7-112180 +371-7-113963	+371-7-112848
Lithuania	Eglė Vagorienė State Medicines Control Agency, Medicines Registration Centre Gedimino ave. 27, 2600 Vilnius	EgleVagoriene@vvkt.lt http://www.vvkt.lt	+370-2-226677	+370-2-313543
Poland	Waldemar Zieliński Drug Institute 30/34 Chelmska Str., 00 725 Warsaw Katarzyna Kazanowska Drug Institute 30/34 Chelmska Str 00 725 Warsaw	waziel@il.waw.pl kazan@il.waw.pl http://www.il.waw.pl/	+48-22-8514381 -8514382 -8412393 -8416743 -8412927, ext. 354 +48-22-8514381 -8412393 -8416743 -8412927, ext. 109	+48-22-8514381 -8514382 -8412393 -8416743 -8412927, ext.199

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Romania	Rodica Badescu National Medicines Agency 48 Aviator Sanatescu Str. 1, 71324 Bucharest	rodica.badescu@anm.kappa.ro http://www.anm.ro	+40-1-2241079	+40-1-224 34 97
Slovak Republic	Dagmar Stara State Institute for Drug Control Kvetna 11, 825 08 Bratislava	stara@sukl.sk http://www.sukl.sk	+421-7-50701143	+421-7-55571944
Slovenia	V. Koblar Agency for Medicinal Products Kersnikova 2, SI-1000 Ljubljana	Vesna.koblar@gov.si http://www.gov.si/mz/amp.htm	+386-1-4786240	+386-1-4786260

Note : the continuously updated list of the EU MS contact points for DP is available on the address:

http://heads.medagencies.org/mrfg/contact/contactpoints.pdf