MINISTRY OF PUBLIC HEALTH

ORDER
on approval of Regulations regarding marketing authorisation and supervision of medicinal products for human use

Taking into account provisions of Law no. 95/2006 on Healthcare Reform, Title XVII “The Medicinal Product", of Government Ordinance no. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved with changes and completions through Law no. 594/2002, with further changes and completions,

on seeing the Approval Report of the Pharmaceutical and Medical Devices Directorate no. E.N. 2.275/20 July 2006,

based on Government Decision no. 862/2006 on organisation and functioning of the Ministry of Public Health,

the minister of public health hereby issues the following order:

Article 1 - Regulations regarding marketing authorisation and supervision of medicinal products for human use are approved as provided in the Annex, which is an integral part of the present order.

Article 2 - The present order shall come into on 28 July 2006, when any other contrary dispositions shall be repealed.

Article 3 - The present order is to be published in the Official Gazette of Romania, Part I.

Minister of public health,
Gheorghe Eugen Nicolăescu

Bucharest, 20 July 2006
Nr. 895

ANNEX

REGULATIONS
regarding marketing authorisation and supervision of medicinal products for human use

CHAPTER I
General provisions

Article 1 – Present regulations have been set up in application of Chapter III "Placing on the Market" and Chapter X "Pharmacovigilance" of Title XVII "The Medicinal Product" of Law 95/2006 on healthcare reform.

Article 2 - (1) Prior to Romania's accession to the European Union, medicinal products for human use may only be placed on the market after grant of a marketing authorisation by the National Medicines Agency.

(2) Following Romania's accession to the European Union, no medicinal product may be placed on the market unless a marketing authorization has been issued by the National Medicines Agency in accordance with these Regulations provisions or an authorisation has been granted according to the centralised procedure.

Article 3 – The marketing authorisation is granted to medicinal products for human use that meet quality, safety and efficacy requirements provided in Article 702 of Law 95/2006.

Article 4 – The National Medicines Agency authorises for placement on the market medicinal products for human use as defined in Article 695, point 1, 3, 4, 5, 9, 30 and 31 of Law 95/2006.

Article 5 - Marketing authorisations can only be granted to an applicant established in Romania (a company formed in accordance with the Romanian law, having its registered office, central administration or principal place of business within Romania) or any other European Union Member State (a company formed in accordance with the law of a Member State and having its registered office, central administration or principal place of business within the Community).

Article 6 – The National Medicines Agency decides on dossier admissibility as well as on granting, modification, suspension or withdrawal of a marketing authorisation for a medicinal product for human use, in line with present Regulations provisions.

Article 7 – Depending on needs, the National Medicines Agency may require external experts for evaluation of the chemical-pharmaceutical and biological, pharmacotoxicological or clinical dossier, in view of marketing authorisation.

CHAPTER II
Submission of applications for marketing authorisation

Article 8 - (1) To commence marketing authorisation procedures for a medicinal product for human use, the Applicant must submit to the National Medicines Agency an Application in the form shown in Annex 1.

(2) The application for marketing authorisation shill be submitted together with documents and information mentioned under Article 702 (4) and (5) of Law 95/2006 and as outlined in Annex I to Order of the Minister of Public Health for approval of analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products (transposing the annex to Directive 2003/63/EC).

(3) In the case of a radionuclide generator, the application for marketing authorisation shall also contain information and details mentioned in Article 703 of Law 95/2006.

Article 9 - (1) In line with cu provisions of Title XVII "The Medicinal Product" of Law 95/2006, the following types of applications for marketing authorisation may be submitted:

a) Application for marketing authorisation based on its own complete documentation including administrative particulars and information on quality, safety and efficacy ("independent" application = "stand-alone" application).

Documents in support of this type of application for marketing authorisation are as mentioned in Article 8 (2) and (3);

b) Applications for marketing authorisation not requiring self – conducted toxicological, pharmacological and clinical studies.

The applicant shall not be required to provide the results of self – conducted pre-clinical and clinical trials if he can demonstrate that:

1. The medicinal product is a generic of a reference medicinal product as outlined in Article 704 (1) and (2) of Law 95/2006 (application for generic medicinal products);

2. The medicinal product contains one or several active substances with well-established medical use, according to Article 705 of Law 95/2006 ("bibliographic" application);

3. The marketing authorisation holder of a reference medicinal product allows the manufacturer use to be made of the pharmaceutical, preclinical and clinical documentation contained in the file on the medicinal product, with a view to examining subsequent applications, according to Article 707 of Law 95/2006 (informed consent application);

c) Applications for marketing authorisation requiring provision of preclinical tests and clinical trial results according to the status of the medicinal product:

1. The medicinal product does not belong to the category of generic medicinal products according to Article 704 (3) of Law 95/2006 (“hybrid” application);

2. Biological medicinal product similar to a reference biological medicinal product not meeting conditions in the definition of generic medicinal products, according to Article 704 (4) of Law 95/2006 (application for similar biological medicinal product);

3. Medicinal products care containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes, according to Article 706 of Law 95/2006 (application for a fixed combination);

4. Traditional herbal medicinal products according to Article 714 of Law 95/2006 (application for traditional herbal medicinal products);

5. Homeopathic medicinal products according to Article 710 of Law 95/2006 (application for homeopathic medicinal products – the applicant submits to the National Medicines Agency an application in the form provided in Annex 2).

Article 10 - (1) Together with the dossier mentioned under Article 8 (2), the applicant also has to submit detailed expert reports in line with Article 709 of Law 95/2006 and Module 2 "Summaries" of Annex I to minister of public health order on approval of analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products.

(2) According to their professional qualification and experience, experts shall:

a) a) Provide detailed reports including their observations on the chemical, pharmaceutical and biological documentation (Module 3), nonclinical documentation (Module 4) and clinical documentation (Module 5), with objective outline of qualitative and quantitative results;

b) Provide observations in line with provisions of Module 2 "Summaries" of Annex I to minister of public health order on approval of analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products;

c) When needed, specify reasons for the use of bibliographic data mentioned under Article 9 (1) b), 2.

Article 11 - (1) For national procedure, a specimen or mock-up of the sales presentation of the medicinal product, together with the proposed package leaflet must be included with the application (the final package to be submitted to the National Medicines Agency following the first production batch after grant of the marketing authorisation) or in packages authorised in their country of origin and presented in a language of international use; in case the medicinal product is presented in several pack sizes, two samples shall be submitted for each pack size.

(2) For biological medicinal product, the application for marketing authorisation shall be accompanied by the necessary number of samples in line with the quality specification for full analysis as well as the summary of batch protocol.

(3) In accordance with provisions of Article 724 b) of Law 95/2006, the evaluator or the Marketing Authorisation Commission may request check of the control methods used by the manufacturer and outlined in quality specifications. If need be in such cases, the applicant shall provide the following for laboratory testing: samples of the finished medicinal product presented in the package it is to be marketed or in mock-up packages, in quantities allowing for verification of the methodology described in the chemical, pharmaceutical and biological particulars accompanying the application, its starting materials, its intermediate products or other constituent materials. Should the medicinal product be presented in several package sizes, laboratory testing shall be performed on the smallest pack size of the medicinal product.

(4) During dossier evaluation, the National Medicines Agency may request inspection of manufacturing site/s and/or preclinical and/or clinical trials site/s by inspectors of the Pharmaceutical inspection department of the National Medicines Agency.

Article 12 - An individual application for marketing authorisation shall be submitted for each different pharmaceutical form and strength of a medicinal product, presented under the same name.

Article 13 - (1) The marketing authorisation/marketing authorisation renewal dossier may be submitted as follows:

- on paper only (one single copy)
- part paper (one single copy for the chemical, pharmaceutical and biological documentation) and part in electronic format (CD) (pharmacotoxicological and clinical documentation).

(2) In case of electronic submission of the dossier, the applicant must also provide a declaration that the content of any reformatted documents is unchanged from initial documentation.

Article 14 – Documentation shall be presented strictly according to the order provided in Annex I to order of the ministry of public health for approval of Analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products.

Article 15 – Dossiers for imported medicinal products may be submitted in Romanian, English or French.

Article 16 - (1) The marketing authorisation fee provided under Article 854 of Law 95/2006 as well as authorisation tariffs established through decision of the Administration Council of the National Medicines Agency, and approved through order of the ministry of public health and published in the Official Gazette of

Romania, Part I, are to be paid in line with payment norms of the National Medicines Agency.

(2) When check of control methods has been necessary, tariffs for laboratory testing established through decision of the Administration Council of the National Medicines Agency, approved through order of the ministry of public health and published in the Official Gazette of Romania, Part I, are to be paid after completion of laboratory testing in question.

(3) If the case may be, the authorisation tariff is regulated at the end of the evaluation procedure.

CHAPTER III
Marketing authorisation procedure

Article 17 - Applicants submit to the Admission of documents/samples compartment of the Evaluation-authorisation department the application for authorisation, the payment form, the authorisation dossier and materials mentioned in Chapter II, according to the type of medicinal product for which authorisation is requested.

Article 18 - The Admission of documents/samples compartment checks whether all required documents are in place, arranged in the requested order and whether requested finished product samples have been submitted, if needed.

Article 19 – Should documentation and materials submitted not comply with present regulations, the application for marketing authorisation is rejected and the reason thereof is entered in the admissions register.

Article 20 – Following payment of authorisation fee and tariff as set in Article 16 (1) and confirmation of their receipt by the Economic department, the authorisation dossier and requested material are distributed to evaluation services.

Article 21 – Within 210 days as of receipt in National Medicines Agency's account of amounts mentioned in Article 20, the Evaluation-authorisation department examines whether the documentation submitted is compliant with provisions of Articles 702, 703, 704, 705, 706 and 707 of Law 95/2006 and whether the conditions for granting a marketing authorisation are satisfied.

Article 22 – Should the submitted dossier be incomplete, the time mentioned under Article 21 is suspended before additional information is provided as requested by the evaluator.

Article 23 – The authorisation dossier evaluation process results in issuance of a final report with recommendation for authorisation or a final report with recommendation for rejection of authorisation.

Article 24 - (1) When laboratory testing is requested in the authorisation procedure according to Article 11 (2), control departments check the control methodology outlined in the documentation; in case of deficiencies and ambiguities, within 30 days as of distribution of documentation to control departments, the applicant is addressed a request for supplementation of particulars provided specifying all requirements from the control department related to methodology and the number of samples, reference substances, impurities, degradation products required for laboratory testing.

(2) Exception to this provision is influenza vaccine under authorisation/renewal procedure, for which check of control methodology and samples shall be organised in such a way as to perform testing as of their submission.

Article 25 – After issuance, complete evaluation reports together with results of laboratory testing if the case may be, are presented in meetings of the Marketing Authorisation Commission, which decides on grant of the marketing authorisation.

Article 26 - According to Article 16 (2) and (3), following expression of favourable opinion by the Marketing Authorisation Commission and confirmation by the Economic department of payment of amounts related to authorisation procedure, the marketing authorisation is written together with the 5 annexes approved by the specialised service within the Evaluation-authorisation department.

Article 27 - The marketing authorisation includes identification data of the medicinal product (registration name, composition, marketing authorisation holder or manufacturer, as the case may be, manufacturers responsible for finished medicinal product batch release, ATC classification, release, packaging, shelf life, storage conditions, marketing authorisation number) and is accompanied by 5 annexes: leaflet, summary of product characteristics, information on labelling, qualitative and quantitative composition, data on medicinal product manufacturing.

Article 28 - (1) Medicinal products authorised for marketing in Romania are entered in the Register of medicinal products authorised in Romania.

2) The marketing authorisation number must be inscribed on the outer packaging of the medicinal product; the number is made up of 3 groups of figures, standing for:

- marketing authorisation number;
- year of authorisation;
- number corresponding to authorised types of packaging.

Article 29 – In the case of influenza vaccine, documentation shall be updated in line with recommendations of the World Health Organisation on circulating strains in the respective season; documentation also includes presentation of clinical trials demonstrating medicinal product efficacy for the current season and is submitted at a date prior to submission of samples for testing.

Article 30 – In circumstances such as provided under Article 730 (10) of Law 95/2006, documentation is returned on applicant request.

CHAPTER IV
Marketing authorisation of medicinal products authorised in the European Union through centralised, mutual recognition, or decentralised procedures

Article 31 - (1) Before Accession, medicinal products authorised in the European Union through centralised, mutual recognition, or decentralised procedures are authorised in Romania through simplified nCADREAC procedures approved through decisions of the Scientific Council of the National Medicines Agency, approved through order of the ministry of public health and published in the Official Gazette of Romania, Part I.

(2) Applications for simplified nCADREAC procedures are submitted according to the following schedule:

- Applications for simplified nCADREAC procedure for medicinal products authorised in the European Union through mutual recognition procedure are only submitted before 31 March 2006;
- Applications for retrospective inclusion in the nCADREAC simplified system for medicinal products authorised through mutual recognition procedure in the European Union and through national procedure in Romania are only submitted before 30 June 2006;
- Applications for simplified nCADREAC procedure for medicinal products authorised in the European Union through centralised procedure are only submitted before 31 August 2006;
- Applications for variations to marketing authorisation and Applications for renewal of marketing authorisation for medicinal products for human use already authorised through CADREAC/nCADREAC simplified procedure for medicinal products authorised in the European Union through centralised procedure and mutual recognition procedure are only submitted before 30 June 2006.

(3) As of Romania’s accession to the European Union, provisions procedures under Title XVII "The Medicinal Product" of Law 95/2006 shall be applied.

CHAPTER **V**
Refusal of application for marketing authorisation

Article 32 – The National Medicines Agency may refuse an application for marketing authorisation of a medicinal product, in line with cu provisions of Article 732 of Law 95/2006.

Article 33 – In the case of a National Medicines Agency unfavourable opinion, the applicant is notified in writing on rejection of the application for marketing authorisation. Refusal is accompanied by a report justifying the decision based on conclusions of evaluation reports.

Article 34 – Within 30 days as of receipt of the refusal report, the applicant may send an appeal that has to be accompanied by detailed justification in its support.

Article 35 – Within 90 days as of receipt of the appeal and justifying documents, the National Medicines Agency must respond on its resolution of the appeal. The solution may be disputed and subjected to administrative law.

CHAPTER **V**I
Marketing authorisation renewal

Article 36 – The marketing authorisation may be renewed on application by the marketing authorisation holder.

Article 37 - (1) In line with Article 730 (2) of Law 95/2006, the application for marketing authorisation renewal is submitted to the National Medicines Agency 6 months prior to expiry of previous authorisation.

(2) The applicant submits an application for marketing authorisation renewal to the National Medicines Agency, in the form presented in Annex 3, the payment form for the fee and tariff according to type of medicinal product, consolidated list of all documents submitted in respect of quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted. Documents are accompanied by finished product samples and, if the case may be, by other material necessary according to Article 11 provisions.

(3) In addition to previously mentioned documents and materials, the dossier of adverse reactions reported during the previous 5 years.

(4) Medicinal products whose authorisation dossier has been updated in accordance with provisions of Order of the ministry of public health no. 92/2006 on amendment and supplementation of Order of the ministry of public health no. 1.451/2005 for approval of the Guidebook regarding update and change of dossiers for authorisation in Romania of medicinal products for human use for compliance with European Community requirements, the applicant submits particulars specified in the application for marketing authorisation renewal.

Article 38 - (1) Stages of procedure for marketing authorisation renewal are the same as presented in Chapter III "Marketing authorisation procedure".

(2) Depending on expiry date of the marketing authorisation granted before entry into force of Law no. 95/2006, the marketing authorisation holder must apply for its renewal as provided in Article 37 (2).

(3) Following marketing authorisation renewal, the manufacturer/holder must see to implementation of previsions mentioned in Article 728 of Law 95/2006.

CHAPTER **V**II
Marketing authorisation suspension and withdrawal

Article 39 – In case of risk to public health, the National Medicines Agency may, on Minister of Public Health request or by referring the matter to itself, suspend or withdraw the marketing authorisation of a medicinal product for human use.

Article 40 - (1) In line with cu Article 828 and 830 of Law 95/2006, the National Medicines Agency shall suspend, withdraw or vary a marketing authorisation of a medicinal product for human use in case of proof of the following:

a) The medicinal product is harmful under normal conditions of use;

b) The medicinal product lacks therapeutic efficacy;

c) The risk-benefit balance is not positive under the normal conditions of use;

d) The medicinal product qualitative and quantitative composition is not as declared;

e) Particulars supporting the application as provided for in Article 702 or Articles 704, 705, 706, 707 and 708 of Law 95/2006 are incorrect or have not been amended in accordance with Article 29;

f) controls carried out on the medicinal product and/or the ingredients and of the controls carried out at an intermediate stage of the manufacturing process, in accordance with the methods laid down in Article 702 (4), i) of Law 95/2006;

g) One of the requirements laid down in Article 749 of Law 95/2006 ceases to be met.

(2) After 3 suspensions of the marketing authorisation, generated by circumstances legitimating its suspension, the marketing authorisation may be withdrawn.

(3) Suspension ceases when circumstances leading to it have been solved.

Article 41 - Marketing authorisation may be also withdrawn in result of request by the medicinal product manufacturer or respective marketing authorisation holder.

Article 42 – After the National Medicines Agency informs the Ministry of Public Health of its decision to suspend or withdraw the marketing authorisation, this shall also notify the marketing authorisation holder and the manufacturer.

CHAPTER **V**III
Supervision of medicinal products for human use

Article 43 - (1) The National Medicines Agency monitors whether efficacy, safety and quality of domestic and imported medicinal products for human use are confirmed in therapeutic use after authorisation for marketing. To this end, the National Medicines Agency shall:

a) receive, through the National Pharmacovigilance System, information from marketing authorisation holders, doctors and other healthcare professionals regarding adverse reactions, intoxications, interactions, resistance development, lack of efficacy, misuse, medicinal product abuse as well as other pharmacovigilance data reported for certain medicinal products for human use authorised for marketing in Romania;

b) Apply, in its pharmacovigilance activity, provisions of guidelines on collection, verification and presentation of adverse reactions according to Article 818 of Law 95/2006;

c) Evaluate and interpret information received on quality, safety and efficacy of medicinal products for human use and propose and administrative measures required according to Article 819 of Law 95/2006;

d) Receive, through the Pharmaceutical inspection department, reports on deficiencies in quality and information related to counterfeited products emerging on Romania's territory.

(2) With the exception of influenza vaccine, for biological products from Pharmaceutical Inspection Cooperation Scheme (PIC/S) member countries, after authorisation, marketing authorisation holders have to submit to the National Medicines Agency the control certificate for the imported batch, issued by competent authorities in the country of origin.

(3) Influenza vaccine undergoes batch-to-batch/bulk-to-bulk control to check the existence of influenza vaccine strains recommended by the World Health organisation. To that purpose, the marketing authorisation holder shall submit to the National Medicines Agency the updated annual documentation, i.e. data on strain characteristics, testing methods, including clinical trial protocols and outcomes, attesting vaccine efficacy for the new season. Manufacturers make available for the National Medicines Agency clinical trial outcomes for the respective season at a date prior to submission for control of the sample meant for use in the respective season.

(4) For biological products from Pharmaceutical Inspection Cooperation Scheme (PIC/S) non-member countries, marketing authorisation holders have to submit samples for each manufacturing batch, for analysis by the National Medicines Agency.

Article 44 – Annexes 1 - 3 are an integral part of the present regulations.

ANNEX No. 1

APPLICATION FOR MARKETING AUTHORISATION OF MEDICINAL PRODUCTS FOR HUMAN USE

SUMMARY OF THE DOSSIER

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APPLICATION FOR MARKETING AUTHORISATION:

ADMINISTRATIVE DATA

The application form is to be used for an application for a marketing authorisation of a medicinal product submitted to the National Medicines Agency under national procedure or nCADREAC simplified procedure.

Separate application is submitted for each strength and pharmaceutical form of the medicinal product for human use.

DECLARATION and SIGNATURE

Name of the medicinal product:

Strength:

Pharmaceutical form:

Active substance(s):

Applicant:

Person authorised on behalf of the Applicant for communication* with the National Medicines Agency, during authorisation procedure:

It is hereby confirmed that all existing data which are relevant to the quality, safety and efficacy of the medicinal product have been supplied in the dossier, as appropriate.
It is hereby confirmed that fees and tariffs will be paid according to the National Medicines Agency payment rules.
On behalf of the Applicant:

_____
Signature

_____
NAME*

_____
Function

_____
Place Date (yyyy-mm-dd)

* ☐ *Note: Please attach letter of authorisation for communication with NMA/ signing on behalf of the applicant.*

This form is intended for use before Accession. After Accession, the form provided in Notice to Applicants shall be used.

1. TYPE OF APPLICATION

Note: The following sections should be completed where appropriate..

1.1. THIS APPLICATION CONCERNS:

❍ 1.1.1. AUTHORISATION UNDER nCADREAC SIMPLIFIED PROCEDURE FOR MEDICINAL PRODUCTS FOR HUMAN USE AUTHORISED IN THE EU UNDER CENTRALISED PROCEDURE

❍ YES ❍ NO

❍ Part A ❍ Part B
Date of acceptance by CHMP:
(yyyy-mm-dd)

λ Rapporteur: λ Co-Rapporteur:
(Name of CHMP Member) (Name of CHMP Member)

❍ 1.1.2. AUTHORISATION UNDER nCADREAC SIMPLIFIED PROCEDURE FOR MEDICINAL PRODUCTS FOR HUMAN USE AUTHORISED IN THE EU UNDER MUTUAL RECOGNITION PROCEDURE

❍ YES ❍ NO

- Reference Member State:
- Date of authorisation: (yyyy-mm-dd):
- Marketing authorisation number:
(a copy of the marketing authorisation shall be provided - see Section 5.2)

- Concerned Member State(s):

AT	☐	BE	☐	CY	☐	CZ	☐	DE	☐	DK	☐	EE	☐	EL	☐
ES	☐	FI	☐	FR	☐	HU	☐	IS	☐	IE	☐	IT	☐	LI	☐
LT	☐	LU	☐	LV	☐	MT	☐	NL	☐	NO	☐	PL	☐	PT	☐
SE	☐	SI	☐	SK	☐	UK	☐								

❍ **1.1.3. <u>UNDER NATIONAL PROCEDURE FOR MEDICINAL PRODUCTS FOR HUMAN USE</u>**

❍ YES ❍ NO

▪ Please specify if a waiver or amendment of PSUR-cycle is applied for, to harmonise with a substance birthdate.

1.2. <u>THIS IS AN APPLICATION FOR A CHANGE TO A MARKETING AUTHORISATION IN PLACE WITH REFERENCE TO ANNEX III OF ORDER OF THE MINISTER OF HEALTH NO. 89/02.02.2004, WHERE APPLICABLE</u>

❍ **YES (***please complete the section below and also complete Section 1.3.)*

❍ **NO (***please complete Section 1.3 only)*

Please specify:

☐ Qualitative change in declared active substance not defined as a new active substance
- ❍ replacement by a different salt/ester, complex/derivative (same therapeutic moiety)
- ❍ replacement by a different isomer, mixture of isomers, of a mixture by an isolated isomer
- ❍ replacement of a biological substance or product of biotechnology
- ❍ new ligand or coupling mechanism for a radiopharmaceutical
- ❍ change to the extraction solvent or the radio of herbal drug to herbal drug preparation

☐ change of bioavailability
☐ change of pharmacokinetics
☐ change or addition of a new strength / potency
☐ change or addition of a new pharmaceutical form
☐ change or addition of a new route of administration

Note:

- The applicant of the present application must be the same as the marketing authorisation holder.
- This section should be completed without prejudice to the provisions of Articles 702 (3), 704 (1), 705, 706, 707 and 726 of Law no. 95/2006 on healthcare reform, <u>Title XVII, The Medicinal Product</u>.

● **<u>For existing marketing authorisation in the Community / Member State where the application is made</u>:**

Name of the marketing authorisation holder
Name, strength, pharmaceutical form of the existing product
Marketing authorisation number(s)

1.3. THIS APPLICATION IS SUBMITTED IN ACCORDANCE WITH THE FOLLOWING ARTICLES OF LAW NO. 95/2006 ON HEALTHCARE REFORM, TITLE XVII, THE MEDICINAL PRODUCT

Note. Section to be completed for any application, including applications referred to in Section 1.2
For further details, please refer to Notice to Applicants, Volume 2A, Chapter 1

1.3.1. ❍ Article 702 (4) application of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, (i.e. Complete dossier with administrative, quality, preclinical and clinical data*)

❍ New active substance
Note: Constituent of a product not yet authorised in Romania

❍ Known active substance
Note: - Constituent of a product already authorised in Romania
- Same or different marketing authorisation holder
*- * For extensions of complete applications, cross references can only be made to preclinical and clinical data.*

1.3.2. ❍ Article 704 (1) and (2) of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product – "generic application"

Note: - Application for a generic medicinal product as defined in Article 704 (2) b) referring to a so-called reference medicinal product with a Marketing authorisation granted in a Member State or in the Community.
- Complete administrative and quality data, appropriate pre-clinical and clinical data when applicable.

■ Reference medicinal product which is or has been authorised for not less than 6/10 years in the European Economic Area (EEA):
- Name of the medicinal product, strength, pharmaceutical form:
- Marketing authorisation holder:
- First authorisation: Date (yyyy-mm-dd) Member State (EEA)/Community:

■ Reference medicinal product authorised in the Community/Member State where the application is made:
- Name of the medicinal product, strength, pharmaceutical form:
- Marketing authorisation holder:
- Marketing authorisation number(s):

■ Medicinal Product used for bioequivalence study, where applicable:
- Name of the medicinal product, strength, pharmaceutical form:
- Marketing authorisation holder:
- Member State of source:

1.3.3. ❍ Article 704 (3) of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product – "hybrid application"

Note: - Application for marketing authorisation for a medicinal product referring to a so-called reference medicinal product with a marketing authorisation in a Member State or in the Community (i.e. different pharmaceutical form, different therapeutic use …).
- Complete administrative and quality data, preclinical and clinical data in accord with regulations (Notice to Applicants, Volume 2A, Chapter 1).

■ Reference medicinal product which is or has been authorised for not less than 6/10 years in EEA:
- Name of the medicinal product, strength, pharmaceutical form:
- Marketing authorisation holder:
- First authorisation: Date (yyyy-mm-dd) Member State (EEA)/Community:

■ Reference medicinal product authorised in the Community/Member State where the application is made:
- Name of the medicinal product, strength, pharmaceutical form:
- Marketing authorisation holder:
- Marketing authorisation number(s):

■ The Medicinal Product used in bioequivalence, where applicable
- Name of the medicinal product, strength, pharmaceutical form:
- Marketing authorisation holder:
- Member State of source:

■ Difference(s) compared to the reference medicinal product:
- ☐ changes in active substance(s)
- ☐ changes in therapeutic use
- ☐ changes in pharmaceutical form
- ☐ changes in strength (quantitative change to active substance(s))
- ☐ changes in route of administration
- ☐ bioequivalence cannot be demonstrated through bioavailability studies

1.3.4. ❍ Article 704 (4) of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product – „similar biological application"

Note: - Application for a product referring to a reference biological product
- Complete administrative and quality data, appropriate pre-clinical and clinical data in accord with regulations (Notice to Applicants, Volume 2A, Chapter 1)

■ Reference medicinal product which is or has been authorised for not less than 6/10 years in the EEA:
- Name of the medicinal product, strength, pharmaceutical form:
- Marketing authorisation holder:
- First authorisation: Date (yyyy-mm-dd) Member State (EEA)/Community:

■ Reference medicinal product authorised in the Community/Member State where the application is made:
- Name of the medicinal product, strength, pharmaceutical form:
- Marketing authorisation holder:

- Marketing authorisation(s) number(s):

- Medicinal Product used for bioequivalence study, where applicable
- Name of the medicinal product, strength, pharmaceutical form:
- Marketing authorisation holder:
- Member State of source:

1.3.5. ❍ Article 705 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product – "well-established use application"

Note: - For further details, please refer to Notice to Applicants, Volume 2A, Chapter1

- For extensions of bibliographical applications, cross references can only be made to preclinical and clinical data

1.3.6 ❍ Article 706 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product – „fixed combination application"

Note: - Complete administrative and quality data, pre-clinical and clinical data on the combination only.

- For extensions of fixed combination applications, cross references can only be made la preclinical and clinical data.

1.3.7. ❍ Article 707 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product – so-called "informed consent application"

Note: - Application for a medicinal product possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form of an authorised product where consent has been given by the existing marketing authorisation holder to use their data in support of this application.

- Complete administrative data should be provided with consent to pharmaceutical, preclinical and clinical data.

- The authorised product and the informed consent application can have the same marketing authorisation holder.

Authorised product in the Community / Member State where the application is made:

- Name of the medicinal product, strength, pharmaceutical form
- Marketing authorisation holder:
- Marketing authorisation number(s):

☐ Attach letter of consent from the marketing authorisation holder of the authorised product (Annex 6.2)

1.3.8 ❍ Article 714 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product – „ application for marketing authorisation for Traditional herbal medicinal product"

Note: - Complete application (see Notice to Applicants, Volume 2A, Chapter 1)

2. MARKETING AUTHORISATION APPLICATION PARTICULARS

2.1. Name(s) and ATC code

2.1.1 Proposed (invented) name of the medicinal product in the Community/Member State/Iceland/Liechtenstein/Norway:

☐ If different (invented) names in different Member States are proposed in a mutual recognition procedure, these are to be listed in Annex 6.18.

2.1.2 Name of the active substance(s):

Note: - Only one name should be given in the following order of priority: International Nonproprietary

Name (INN), European Pharmacopoeia, the Romanian Pharmacopoeia, common name scientific name;*

*- *The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant (for further details, consult the Guideline on the SPC)*

2.1.3 Pharmacotherapeutic group (Please use current ATC code):

ATC code: **Pharmacotherapeutic group:**

If no ATC code has been assigned, please indicate if an application for ATC code has been made: ☐

2.2. Pharmaceutical form, strength, route of administration, container and pack size(s)

2.2.1 Pharmaceutical form and strength (please use current list of standard terms - European Pharmacopoeia)

***Pharmaceutical form*:**
Active substance(s) ***Strength(s):***

2.2.2 Route of administration (please use current list of standard terms according to European Pharmacopoeia)

2.2.3 Container, closure and administration device(s), including description of material from which it is constructed (please use current list of standard terms - European Pharmacopoeia)

For each type of pack, please give:

2.2.3.1 Package size(s):
Note: - For mutual recognition and decentralised procedures, all package sizes authorised in the Reference Member should be listed

2.2.3.2 Proposed shelf life:

2.2.3.3 Proposed shelf life (after first opening container):

2.2.3.4 Proposed shelf life (after reconstitution or dilution):

2.2.3.5 Proposed storage conditions:

2.2.3.6 Proposed storage conditions after first opening:

☐ Attach list of Mock-ups or Samples/specimens sent with the application, as appropriate.

2.3 Legal status

2.3.1 Proposed dispensing/classification

(Classification under Article 695 (19) of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product)

❍ Subject to medical prescription

❍ Not subject to medical prescription

2.3.2 For medicinal products subject to medical prescription:

☐ Medicinal product on prescription which may be renewed (if applicable)
☐ Medicinal product on prescription which may not be renewed (if applicable)
☐ Medicinal product on special prescription*
☐ Medicinal product on restricted prescription*

Applicants are required to indicate which categories they are requesting, however, the NMA reserves the right to apply only those categories provided for in Law no. 95/ 2006 on healthcare reform, Title XVII, The Medicinal Product.

**Note: - For further information, please refer to Article 781 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product.*

2.3.3 Supply for products not subject to medical prescription

❍ Supply through pharmacies only

❍ Supply through non-pharmacy outlets and pharmacies (if applicable)

2.3.4 Promotion for products not subject to medical prescription

❍ Promotion to health care professionals only

❍ Promotion to the general public and health care professionals

2.4. Marketing authorisation holder/Contact person/Company

2.4.1 Proposed marketing authorisation holder/person legally responsible for placing the product on the market in Romania

(Company) Name:
Address:
Country:
Telephone:
Telefax:
E-Mail:
Contact person at this address:

☐ Attach proof of establishment of the applicant in Romania or the European Economic Area (Annex 6.3)

2.4.2 Person/Company authorised for communication with the National Medicines Agency during authorisation procedure in Romania:

Name:
Company name:

☐ If different from pct. 2.4.1 above, attach letter of authorisation (Annex 6.4)

Address:
Country:
Telephone:
Telefax:
E-Mail:

2.4.3 Person/Company authorised for communication between the marketing authorisation holder and the National Medicines Agency, after authorisation, in Romania, If different from Person/Company under 2.4.2

Name:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

☐ If different from 2.4.1 above, please attach letter of authorisation (Annex 6.4)

2.4.4 Qualified person in Romania for Pharmacovigilance

Name:
Company name:
Address:
Country:
24 H Telephone:
Telefax:
E-Mail:

☐ Attach C.V. of qualified person (Annex 6.5)

2.4.5 Person in charge of scientific service of the marketing authorisation holder in Romania as referred to in Article 809 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product

Name of contact person:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

2.5 Manufacturers

Note: ALL manufacturing and control sites mentioned throughout the whole dossier MUST have references regarding their names, detailed addresses and activities.

2.5.1 Authorised manufacturer(s) (or importer) responsible for batch release in Romania in accord with Articles 748 and 760 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product:

Company name:
Address:
Country:

Telephone:
Telefax:
E-Mail:

- Manufacturing Authorisation number:
- ☐ Attach copy of manufacturing authorisation(s) (Annex 6.6)
- ☐ Attach justification if more than one manufacturer responsible for batch release are proposed (Annex 6.7)

For Blood Products and Vaccines:

Details of the state laboratory or laboratory designated for that purpose where the official batch release takes place (in accordance with Articles 823 (1), 825, 826 (1) and (2) and Article 827 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, for products authorised in the EEA)

Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

2.5.1.1 Contact person in the EEA for product defects and recalls, as defined in Article 790 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product (for decentralised procedure only)

Name:
Address:
Country:
Telephone 24 H:
Telefax:
E-Mail:

2.5.1.2 Batch control/Testing arrangements

Site(s) in EEA or in countries where an mutual recognition agreement or other Community arrangements apply where batch control/testing takes place (if different

from 2.5.1., as required by Article 760 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product):

Company name:
Address:
Country:
Telephone:
Telefax:
E-mail:

Please provide brief description of control test carried out by the laboratory(ies) concerned.

2.5.2 Manufacturer(s) of the medicinal product and site(s) of manufacture (including manufacturing sites of any diluent/solvent presented in a separate container but forming part of the medicinal product)

Name:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

Please provide brief description of functions performed by manufacturer of dosage form/assembler etc.:

☐ Attach flow-chart indicating the sequence and activities of the different sites involved in the manufacturing process, including testing sites (Annex 6.8)

- If the manufacturing site is in the EEA:
  - Manufacturing Authorisation number
  - ☐ Attach manufacturing authorisations required under Article 748 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product (Annex 6.6)
  - Name of qualified person:
    (if not mentioned in manufacturing authorisation)

- If the manufacturing site is outside the EEA:
  - ☐ Where MRA or other Community arrangements apply, attach equivalent of manufacturing authorisation (Annex 6.6)
  - The site has been inspected for GMP Compliance by an EEA authority or by an authority of countries where MRA or other Community arrangements apply within the terms of the agreement.

❍ YES ❍ NO

☐ If yes, please provide in Annex 6.9, for each site, a statement from the competent authority
which carried out the inspection, including:
- Last GMP inspection date
- Name of competent authority which carried out the inspection
- Category of products and activities inspected
- Outcome: GMP compliant: ❍ YES ❍ NO

- The site has been inspected for GMP Compliance by any other authority including those of
countries where MRA or other Community arrangements apply but not within the respective
territory?

❍ YES ❍ NO

☐ If YES, please provide summary information in Annex 6.9

Including: - Last GMP inspection date (yyyy-mm-dd)
- Name of competent authority which carried out the inspection
- Category of products and activities inspected
- Outcome: ❍ Positive ❍ Negative

2.5.3 Manufacturer(s) of the active substance and site(s) of manufacture

Note: - All manufacturing sites involved in the manufacturing process of each source of active substance should be listed. For biotech products, include all sites of storage of master and working cell bank and preparation of working cell banks.

Substance:
Name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

Please provide brief description of manufacturing steps performed by manufacturing site:

• The European Pharmacopoeia has issued a Certificate of suitability for the active substance(s)

❍ YES ❍ NO

If YES, please specify:
- Substance:
- name of the manufacturer:

- reference number:
- Date of last update (*yyyy-mm-dd*):

☐ Please provide copy in Annex 6.10

• An Active Substance Master File (Drug Master File - DMF) is to be used for the active substance

❍ YES ❍ NO

If YES, please specify

- Substance:
- Name of the manufacturer:
- Reference number for EMEA/competent authority:
- Date of submission (*yyyy-mm-dd*):
- Date of last update (*yyyy-mm-dd*):

☐ Please attach letter of access for Community/Member State authorities where the application is made (please refer to European DMF procedure) (Annex 6.10)

☐ Please attach copy of written confirmation from the manufacturer of the active substance to inform the applicant in case of modification of the manufacturing process or specifications according to Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product (Annex 6.11)

• There is an EMEA certificate for a Vaccine Antigen Master File (VAMF) issued or submitted in accordance with Directive 2001/83/EC Annex I, Part III, being used for this application for marketing authorisation

❍ YES ❍NO

If YES, please specify:

- Substance name:
- Name of the VAMF Certificate Holder/VAMF Applicant:
- Reference number of Application/ Certificate:
- Date of submission (if pending) (*yyyy-mm-dd*):
- Date of approval or last update (if approved) (*yyyy-mm-dd*):

☐ Please attach copy in Annex 6.19

(Section to be copied/completed as per however many VAMFs may be cross-referenced)

Where an active substance manufacturer has been inspected by an EEA Country

☐ *The following information is provided in Annex 6.9 for each manufacturing site:*

- *Last inspection date by an EEA country (yyyy-mm-dd*)
- *Name of competent authority which carried out the inspection*
- *Type of inspection (pre/post-authorisation/special/re-inspection)*
- *Categories of ingredients and activities inspected*
- *Outcome:* ❍ *Positive* ❍*Negative*

2.5.4 Contract companies used for clinical trial(s) on bioavailability or bioequivalence or used for the validation of blood product manufacturing processes.

For each contract company, specify the state where analytical tests have been performed and where clinical data are collected and given:

Title of the study:
Protocol code:
EudraCT-Number:
Company name:
Address:
Country:
Telephone:
Telefax:
Email:
Duty performed according to contract:

2.6 Qualitative and quantitative composition

2.6.1 Qualitative and quantitative composition – Active substance(s) and excipient(s):

A note is to be given as to which quantity the composition refers (e.g. 1 capsule)
Please list the active substance(s) separately from the excipient(s).

Name of active substance(s)	Quantity	Unit	Reference/ Monograph standard

etc.

Name of excipient(s)/*	Quantity	Unit	Reference/Monograph standard

etc.

*Note: * Only one name for each substance should be given in the following order of priority: INN**, European Pharmacopoeia, Romanian Pharmacopoeia, Common name, Scientific name*
***The active substance should be declared by its recommended INN accompanied by its salt or hydrate form if relevant*

Details of any overages are stated below:
- Active substance:

- excipient(s):

2.6.2 List materials of animal and/or human origin contained or used in the manufacturing process of the medicinal product

NONE ☐

Name	Function* AS	EX	R	Animal origin susceptible to TSE**	Other animal origin	Human origin	Certificate of suitability for EST (state number)
1.	❍	❍	❍	❍	❍	❍	❍
2.	❍	❍	❍	❍	❍	❍	❍
3.	❍	❍	❍	❍	❍	❍	❍
4.	❍	❍	❍	❍	❍	❍	❍

etc.

* AS= Active substance, EX = excipient (including starting materials used in the manufacture of the active substance/excipient) R= reagent/culture medium (including those used in the preparation of master and working cell banks)

** EST = transmissible spongiform encephalopathy

☐ If a European Pharmacopoeia Certificate of Suitability for TSE is available according to Resolution AP/CSP (99)4 of the Council of Europe, please attach in Annex 6.12

2.6.3 There is an EMEA certificate for a Plasma Master File (PMF) issued or submitted in accordance with Directive 2001/83/EC Annex I, Part III, being used for this application for marketing authorisation

❍ YES ❍ NO

If YES, please give:

- Substance referring to PMF:

function* AS	EX	R
❍	❍	❍

- Name of the PMF Certificate Holder/ PMF applicant:
- Number of Application/ Certificate:
- Date of submission (if pending) (*yyyy-mm-dd*):
- Date of approval or last update (if approved) (*yyyy-mm-dd*):

☐ Please provide copy in Annex 6.20

* SA = Active substance, EX = excipient (including starting materials used in the manufacture of the active substance/excipient), R = reagent/culture medium (including those used in the preparation of master and working cell banks)

(Section to be copied/completed as per however many PMFs may be cross-referenced)

2.6.4 The medicinal product contains or consists of genetically modified organisms within the meaning of Directive 2001/18/EC

❍ YES ❍ NO

If YES, the product complies with Directive 2001/18/EC:

❍ YES ❍ NO

☐ Please a*ttach a copy of any written consent(s) of the competent authorities to the deliberate release into the environment of the Genetically Modified Organisms for research and development purposes where provided for by Part B of the above-mentioned Directive (Annex 6.13)*

3. SCIENTIFIC ADVICE

3.1. Formal scientific advice has been given by the CHMP for this medicinal product:

❍ YES ❍ NO

If YES, please give:

Date (*yyyy-mm-dd*):
References:
☐ Please attach copy of the scientific letter (Annex 6.14)

3.2. Scientific advice has been given by Member State(s) for this medicinal product:

❍ YES ❍ NO

If YES,

Member State(s): Date (*yyyy-mm-dd*):

4. PAEDIATRIC DEVELOPMENT PROGRAMME

4.1. There is a paediatric development programme for this medicinal product:

❍ YES

❍ NO

Please indicate the relevant section(s) in the dossier if included:

5 OTHER MARKETING AUTHORISATION APPLICATIONS

5.1 FOR NATIONAL APPLICATIONS ONLY, PLEASE COMPLETE THE SECTION BELOW, IN ACCORDANCE WITH ARTICLE 702 LIT. m)-o) OF LAW NO. 95/2006 ON HEALTHCARE REFORM, TITLE XVII, THE MEDICINAL PRODUCT:

5.1.1 There is/are other Member State(s) where an application for the same medicinal product is pending*.

❍ YES ❍ NO

If YES, please complete Section 5.2.

5.1.2 There is/are other Member State(s) where an authorisation is granted for the same medicinal product.**

❍ YES ❍ NO

If YES, Section 5.2 must be completed and copy of authorisation provided.

There are differences which have therapeutic implications between this application and the applications/authorisations for the same product in other Member States (for national applications, in accord with Article 722 or Article 723 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product).

❍ YES ❍ NO

If YES, please elaborate:

5.1.3 There is/are other Member State(s) where an authorisation has been refused/ suspended/ revoked by competent authorities for the same* medicinal product.

❍ YES ❍ NO

If YES, please complete Section 5.2

**Note: "same product" means same qualitative and quantitative composition in active substance(s)*

and having the same pharmaceutical form from applicants belonging to the same mother company

or group of companies OR which are "licensees".

5.2. Marketing authorisation applications for the <u>same</u> product in the EEA (e.g. *medicinal products with* same *qualitative and quantitative composition in active substance(s) and having the same pharmaceutical form from applicants belonging to the same mother company or group of companies OR*

which are "licensees".

Note: Please refer to Commission Communication 98/C229/03

☐ <u>Countries which have authorised the medicinal product:</u>

Country:

Date of authorisation (*yyyy-mm-dd*):

Invented name:

Authorisation number:

☐ Please provide copy of the marketing authorisation (Annex 6.15)

☐ <u>Countries in which authorisation of the medicinal product is pending</u>

Country:

Date of submission (*yyyy-mm-dd*):

☐ <u>Countries in which authorisation of the medicinal product has been refused</u>

Country:

Date of refusal (*yyyy-mm-dd*):

☐ <u>Countries in which authorisation of the medicinal product has been withdrawn (by the Applicant, before authorisation)</u>

Country:

Date of withdrawal (*yyyy-mm-dd*):

Invented name:

Reason for withdrawal:

☐ <u>Countries in which authorisation of the medicinal product has been withdrawn (by the Applicant, after authorisation)</u>

Country:

Date of withdrawal (*yyyy-mm-dd*):

Authorisation number:

Invented name:

Reason for withdrawal:

☐ <u>Countries whose competent authorities have suspended /revoked authorisation of the medicinal product</u>

Country:

Date of suspension/revocation (*yyyy-mm-dd*):

Reason for suspension/revocation:

Invented name:

5.3 <u>For multiple applications of the same medicinal product:</u>

Multiple applications for:

Name of the other product(s):

Date of application(s) (*yyyy-mm-dd*):

Applicant(s):

☐ Please attach copy of correspondence with the European Commission, for centralised procedures only (Annex 6.16)

5.4 Marketing authorisation applications for <u>the same</u> product outside the EEA (*i.e. from applicants belonging to the same mother company or group of companies OR which are "licensees")*

Note: Please refer to Commission Communication 98/C229/03

☐ <u>Countries which have authorised the medicinal product</u>

Country:

Date of authorisation (*yyyy-mm-dd*):

Invented name:

☐ <u>Countries in which authorisation of the medicinal product is pending</u>

Country:

Date of submission (*yyyy-mm-dd*):

☐ <u>Countries in which authorisation of the medicinal product has been refused</u>

Country:

Date of refusal (*yyyy-mm-dd*):

☐ <u>Countries in which authorisation of the medicinal product has been withdrawn (by the Applicant before authorisation)</u>

Country:

Date of withdrawal (*yyyy-mm-dd*):

Invented name:

Reason for withdrawal:

☐ <u>Countries in which authorisation of the medicinal product has been withdrawn (by the Applicant after authorisation)</u>

Country:

Date of withdrawal (*yyyy-mm-dd*):

Authorisation number:

Invented name:

Reason for withdrawal:

☐ Countries whose competent authorities have suspended /revoked authorisation of the medicinal product

Country:

Data date of suspension/revocation (*yyyy-mm-dd*):

Reason for suspension/revocation:

Invented name:

6. ANNEXED DOCUMENTS (WHERE APPROPRIATE)

☐ **6.1** Proof of payment

☐ **6.2** Consent of the Marketing Authorisation Holder for the reference medicinal product who allows an applicant to make use of the pharmaceutical, preclinical and clinical documentation contained in the file on the medicinal product, with a view to examining subsequent applications (for informed consent marketing authorisation applications)

☐ **6.3** Proof of establishment of the applicant in the EEA.

☐ **6.4** Letter of authorisation for communication on behalf of the applicant/marketing authorisation holder.

☐ **6.5** Curriculum Vitae of the Qualified Person for Pharmacovigilance

☐ **6.6** Manufacturing Authorisation required under Article Article 748 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product (or equivalent, outside of the EEA where MRA or other Community arrangements apply). A reference to EudraGMP will suffice when available**.**

☐ **6.7** Justification for more than one manufacturer responsible for batch release in the EEA.

☐ **6.8** Flow-chart indicating all sites involved in the manufacturing process of the medicinal product or active substance (including sites involved in sampling and testing for batch release of products manufactured in third countries). ALL manufacturing and control sites mentioned throughout the whole dossier MUST be consistent regarding their names, detailed addresses and activities.

☐ **6.9** Statement (or GMP Certificate issued by an EEA inspectorate, when available) from the competent authority which carried out the inspection of the manufacturing site(s)/(not older than 3 years). References to EudraGMP will suffice when available. Where applicable a summary of other GMP inspections performed in the last 2 years.

☐ **6.10** Letter(s) of access to Active Substance Master File(s) or copy of European Pharmacopoeia Certificate(s) of suitability.

☐ **6.11** Copy of written confirmation from the manufacturer of the active substance to inform the applicant in case of modification of the manufacturing process or specifications according to Annex I to order of the ministry of health on approval of ”Analytical, pharmacotoxicological and clinical

norms and protocols in respect of the testing of medicinal products" (transposing Annex I of Directive 2001/83)

☐ **6.12** European Pharmacopoeia Certificate(s) of suitability for TSE.

☐ **6.13** Written consent(s) of the competent authorities regarding genetically modified organisms release in the environment.

☐ **6.14** Scientific advice given by CHMP.

☐ **6.15** Copy(ies) of Marketing Authorization(s) granted in an EEA country or third country under Article 702, m)-o) of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product and the equivalent in third countries on request (photocopies of the pages which give the Marketing authorisation number, Date of authorisation and pages which have been signed by the competent authorities).

☐ **6.16** Correspondence with European Commission regarding multiple applications.

☐ **6.17** List of Mock-ups or Samples/specimens sent with the application, as appropriate.

☐ **6.18** List of proposed (invented) names and marketing authorisation holders in the concerned member states.

☐ **6.19** Copy of EMEA certificate for a Vaccine Antigen Master File (VAMF)

☐ **6.20** Copy of EMEA certificate for Plasma Master File (PMF)

☐ **6.21** For each active substance, attach a declaration from the Qualified Person of the manufacturing authorisation holder authorisation holder of each of the manufacturing authorisation holders (i.e. located in EEA listed in Section 2.5.2 where the active substance is used as a starting material that the active substance manufacturer(s) referred to in Section 2.5.3 operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. This does not apply to blood or blood components.

ANNEX No. 2

APPLICATION FOR MARKETING AUTHORISATION OF HOMEOPATHIC MEDICINAL PRODUCTS FOR HUMAN USE

SUMMARY OF THE DOSSIER

●●●●●

APPLICATION FOR MARKETING AUTHORISATION:

ADMINISTRATIVE DATA

The application form is to be used for an application for a marketing authorisation of a medicinal product submitted to the National Medicines Agency under national procedure or new CADREAC simplified registration procedures.

Separate application is submitted for each strength and pharmaceutical form of the medicinal product for human use.

DECLARATION AND SIGNATURE:

Invented name:

Pharmaceutical form:

Homeopathic stock(s) and potency(ies):

Applicant:

Person authorised on behalf of the Applicant for communication* with the National Medicines Agency, during authorisation procedure:

It is hereby confirmed that all existing data which are relevant to the quality, safety and efficacy of the medicinal product have been supplied in the dossier, as appropriate.
It is hereby confirmed that fees will be paid according to the National Medicines Agency rules.
On behalf of the Applicant:

_____
Signature

_____
NAME*

_____
Function

_____
Place Date (year-month-day)

** Note: Please attach letter of authorisation for communication with NMA/signing on behalf of the applicant.*

1. TYPE OF APPLICATION

Note: The following sections should be completed where appropriate..

1.1. THIS APPLICATION CONCERNS:

1.1.1. nCADREAC SIMPLIFIED REGISTRATION PROCEDURE FOR MEDICINAL PRODUCTS FOR HUMAN USE AUTHORISED IN THE EU UNDER MUTUAL RECOGNITION PROCEDURE

❍ **YES** ❍ **NO**

- Reference Member State:
- Date of authorisation: (year-month-day):
- Marketing authorisation number:
  (please provide copy of the authorisation – see Section 5.2)

- Member State(s)/Concerned Member State(s):

AT	☐	BE	☐	CY	☐	CZ	☐	DE	☐	DK	☐	EE	☐	EL	☐
ES	☐	FI	☐	FR	☐	HU	☐	IE	☐	IS	☐	IT	☐	LI	☐
LT	☐	LU	☐	LV	☐	MT	☐	NL	☐	NO	☐	PL	☐	PT	☐
SE	☐	SI	☐	SK	☐	UK	☐								

❍ **1.1.2. NATIONAL PROCEDURE**

❍ YES ❍ NO

- Please specify If a waiver or amendment of PSUR-cycle is applied for, to harmonise with a substance birthdate:

1.2. THIS IS AN APPLICATION FOR VARIATION TO A MARKETING AUTHORISATION IN PLACE WITH REFERENCE TO ANNEX III OF ORDER OF THE MINISTER OF HEALTH NO. 89/02.02.2004, WHERE APPLICABLE

❍ **YES** *(please complete the section below and Section 1.3.)*

❍ **NO** (*please complete Section 1.3 only)*

Please give:

☐ Qualitative change in declared active substance not defined as a new active substance

❍ Replacement by a different salt/ester, complex/derivative (same therapeutic moiety)
❍ Replacement by a different isomer, mixture of isomers, of a mixture by an isolated isomer
❍ Replacement of a biological substance or product of biotechnology
❍ New ligand or coupling mechanism for a radiopharmaceutical
❍ Change to the extraction solvent or the radio of herbal drug to herbal drug

☐ Change of bioavailability
☐ Change of pharmacokinetics
☐ Change or addition of a new strength / potency
☐ Change or addition of a new pharmaceutical form
☐ Change or addition of a new route of administration

Note:
The applicant of the present application must be the same as the marketing authorisation holder of the existing marketing authorisation
This section should be completed without prejudice to the provisions of Articles 702 (1) and (4), 704 (1), 708 (1) and (7) and 726 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product

● **For existing marketing authorisation in the Community / Member State where the application is made:**
- Name of the marketing authorisation holder:
- Name, strength, pharmaceutical form of the existing product:
- Marketing authorisation number:

1.3. APPLICATION FOR MARKETING AUTHORISATION SUBMITTED UNDER THE FOLLOWING ARTICLES OF LAW NO. 95/2006 ON HEALTHCARE REFORM, TITLE XVII, THE MEDICINAL PRODUCT

Note: Section to be completed for any application, including applications referred to in Section 1.3

❍**1**.3.1 Article 711 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product (simplified registration procedure)

❍**1**.3.2 Article 713 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product (marketing authorisation procedure)

1.4 Administrative data/dossier requirements

Article 711 - Simplified registration procedure

Part of the dossier	Submitted in the Application dossier	
Module 1	❍	

Manufacturing license	❍	
Mock ups of outer and immediate packaging and of package leaflet	❍	
Module 2	❍	
Module 3	❍	
Module 4	❍	
Justification of the homeopathic nature	❍	

Article 713 – Marketing authorisation procedure

Part of the dossier	Submitted in the Application dossier	
Module 1	❍	
Manufacturing license	❍	
SPC in National language	❍	
Package leaflet in National language	❍	
Mock ups of outer and immediate packaging and of package leaflet	❍	
Module 2	❍	
Module 3	❍	
Module 4	❍	
Justification of the homeopathic nature	❍	

2. MARKETING AUTHORISATION/REGISTRATION APPLICATION PARTICULARS

2.1. Name (s)

2.1.1 Name of the homeopathic medicinal product

☐ If different (invented) names in different Member States are proposed in a mutual recognition, these are to be listed in Annex 4.18

2.1.2 Name of the Homeopathic stock(s) and potencies[1]

[1] *The following order of priority should be used: Scientific name of the European Pharmacopoeia or National Pharmacopoeia or, in absence of a monograph, a Scientific Latin name (botanical scientific name) followed by the Homeopathic(s) name(s).*

2.2. Pharmaceutical form, route of administration, container and pack size(s)

2.2.1 Pharmaceutical form (please use current list of standard terms according to European Pharmacopoeia)

2.2.2 Route(s) of administration (use current list of standard terms according to European Pharmacopoeia)

2.2.3 Container, closure and administration device(s), including description of material from which it is constructed (**use current list of standard terms according to European Pharmacopoeia**)

For each type of pack give:

2.2.3.1 Pack size(s):

Note: For mutual recognition and decentralised procedures, all package sizes authorised in the Reference Member should be listed

2.2.3.2 Proposed shelf life:

2.2.3.3 Proposed shelf life (after first opening container):

2.2.3.4 Proposed shelf life (after reconstitution or dilution):

2.2.3.5 Proposed storage conditions:

2.2.3.7 Proposed storage conditions after first opening container:

☐ Please attach list of mock-ups or samples/specimens sent with the application, as appropriate (please refer to Notice to Applicants, Volume 2A, Chapter 7) (4.17)

2.4 Legal status

2.3.1 Proposed dispensing/classification

(Under Article 695 (19) of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product)

❍ Subject to medical prescription

❍ Not subject to medical prescription

2.3.2 For products subject to medical prescription:

☐ Product on prescription which **may be** renewed (if applicable)
☐ Product on prescription which **may not be** renewed (if applicable)
☐ Product on **special** prescription*****
☐ Product on **restricted** prescription*****

Applicants are invited to indicate which categories they are requesting, however, the NMA reserve the right to apply only those categories provided for in Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product

**Note: for further information please refer to Article 781 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product*

2.3.3 Supply for products not subject to medical prescription:

❍ Supply through pharmacies only

❍ Supply through non-pharmacy outlets and pharmacies(if applicable)

2.3.4 Promotion for products not subject to medical prescription:

❍ Promotion to health care professionals only

❍ Promotion to the general public and health care professionals

2.4. Marketing authorisation holder/Person de contact/Company

2.4.1 Proposed marketing authorisation holder/person legally responsible for placing the product on the market in Romania

(Company) Name:
Address:
Country:
Telephone:
Telefax:
E-Mail:
Contact person at this address

☐ Please attach proof of establishment of the applicant in Romania or The European Economic Area (EEA) (Annex 4.3)

2.4.2 Person/Company authorised for communication with the National Medicines Agency during authorisation procedure in Romania:

Name:
of
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

☐ If different from 2.4.1 above, please attach letter of authorisation (Annex 4.4)

2.4.3 Person/Company authorised for communication between the marketing authorisation holder and the National Medicines Agency, after authorisation in Romania, if different from Person/Company under 2.4.2

Name:
letter of
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

☐ If different from 2.4.1 above, , please attach authorisation (Annex 4.4)

2.4.4 Qualified person in Romania for Pharmacovigilance

Name:
Company name:
Address:
Country:
24 H Telephone:
Telefax:
E-Mail:

☐ Please provide C.V. of qualified person (Annex 4.5)

2.5 Manufacturers

2.5.1 Authorised manufacturer(s) (or importer) responsible for batch release in Romania in accordance with Articles 748 and 760 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product **(**as shown in the package leaflet and where applicable in the labelling):

Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

- Manufacturing Authorisation number:
- ☐ Attach copy of manufacturing authorisation(s)(Annex 4.6)
- ☐ Attach justification if more than one manufacturer responsible for batch release is proposed with product batch release (Annex 4.7)

2.5.1.1 Batch control/Testing arrangements

Site(s) in EEA or in countries with MRA/another agreement in operation, where batch control/testing takes place (if different from 2.5.1):

Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

2.5.2 Manufacturer(s) of the homeopathic medicinal product and Site(s) of manufacture

(Note: Please give including manufacturing sites of any diluent/solvent presented in a separate container but forming part of the Homeopathic medicinal product):

Name:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:
Please provide brief description of functions performed by manufacturer of dosage form/assembler etc.:

☐ Please attach flow-chart indicating the sequence of the different sites involved in the manufacturing process (Annex 4.8)

• If the manufacturing site is in the EEA:

- Manufacturing Authorisation number

(under Article 748 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product):

☐ Please attach copy of manufacturing authorisation (s) (Annex 4.6)

- Name of qualified person

(if not mentioned in manufacturing authorisation)

• If the manufacturing site is outside the EEA:

- ☐ Where MRA/another community agreement is in operation, attach equivalent of manufacturing authorisation (Annex 4.6)

- The site has been inspected for GMP Compliance by an EEA authority or by an authority of

countries where mutual recognition agreement /another community agreement is in operation

❍ YES ❍ NO

☐ If YES, please provide in Annex 4.9, for each site, a statement from the competent authority which carried out the inspection, including:

- Last GMP inspection date
- Name of competent authority which carried out the inspection
- Type of inspection (pre/post-authorisation/special/re-inspection)
- Category of products and activities inspected
- Outcome: GMP compliant : ❍ NO ❍ YES

2.5.3 Manufacturer (s) of the dilutions and Site(s) of manufacture

(Note: If different from manufacturer of the finished homeopathic medicinal product):

Name:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

Please provide brief description of functions performed by manufacturer of dosage form/assembler etc.:

☐ Please attach flow-chart indicating the sequence of the different sites involved in the manufacturing process (Annex 4.8)

• If the manufacturing site is in the EEA:

- Manufacturing Authorisation number
(under Article 748 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product):
☐ Please attach copy of manufacturing authorisation (s) (Annex 4.6)

- Name of qualified person:
(if not mentioned in manufacturing authorisation)

• If the manufacturing site is outside the EEA:

- ☐ Where MRA/another community agreement is in operation, attach equivalent of manufacturing authorisation (Annex 4.6)

- The site has been inspected for GMP Compliance by an EEA authority or by an authority of countries where MRA/another community agreement is in operation

❍ YES ❍ NO

☐ If YES, please provide in Annex 4.9, for each site, a statement from the competent authority which carried out the inspection, including:

- Last GMP inspection date
- name of competent authority which carried out the inspection
- type of inspection (pre/post-authorisation/special/re-inspection)
- category of products and activities inspected
- outcome: GMP compliant: ❍ YES ❍ NO

2.5.4 Manufacturer(s) of the Homeopathic stock(s):

Note: Only the final manufacturer(s) to be mentioned

Substance:
Name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

• A European Phaemacopoea Certificate of suitability has been issued for the active substance(s)

❍ YES ❍ NO

If YES, please specify:

- Substance:
- Name of the manufacturer:
- Reference number:
- Date of last update (*yyyy-mm-dd*):

☐ Please provide copy in Annex 4.10

• There is a European Drug Master File to be used for the active substance(s) reference/original

❍ YES ❍ NO

If YES, please specify:

- Substance:
- Name of the manufacturer:
- Reference number for EMEA/competent authority:
- Date of submission (*yyyy-mm-dd*):
- Date of last update (*yyyy-mm-dd*):
- ☐ Please attach letter of access for Community/Member State authorities where the application is made (please refer to European DMF procedure for active substance) (Annex 4.10)
- ☐ Please attach copy of written confirmation from the manufacturer of the active substance to inform the applicant in case of modification of the manufacturing process or specifications according to Article Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product. (Annex 4.11)

Where an active substance manufacturer has been inspected by an EEA Country

☐ *The following information is provided in Annex 4.9 for each manufacture site*

- *Last inspection date by an EEA country (year-month-day*)
- *Name of competent authority which carried out the inspection*
- *Type of inspection (pre/post-authorisation/special/re-inspection)*
- *Categories of substance and activities inspected*
- *Outcome:* ❍*Positive* ❍*Negative*

2.5.5 Source/manufacturer(s) of the raw material(s):

Raw material:
Name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

• A European Pharmacopoeia Certificate of suitability has been issued for the raw material(s)

❍ YES ❍ NO

If YES, please specify:
- Raw material:
- Name of the manufacturer:
- Reference number:
- Date of last update (*yyyy-mm-dd*):
☐ Please provide copy in Annex 4.10

Where an active substance manufacturer has been inspected by an EEA Country
☐ *The following information is provided in Annex 4.9 for each manufacture site*
- *Last inspection date by an EEA country (yyyy-mm-dd)*
- *Name of competent authority which carried out the inspection*
- *Type of inspection (pre/post-authorisation/special/re-inspection)*
- *Categories of substance and activities inspected*
- *Outcome:* ❍*Positive* ❍*Negative*

2.6 Qualitative and quantitative composition

2.6.1 Qualitative and quantitative composition in terms of the homeopathic active substance(s) and the excipient(s):

A note should be given as to which quantity the composition refers (e.g. 1 capsule)
List the homeopathic active substance(s) separately from the excipient(s).

Name of homeopathic active substance(s)*	Quantity	Unit	Reference/ Monograph standard
1.			
2.			
3.			
etc.			

Name of excipient (s)	Quantity	Unit	Reference/Standard Monograph**
1.			
2.			
3.			
etc.			

*Note: *The following order of priority should be used: Scientific Latin name of the European Pharmacopoeia or of the Romanian Pharmacopoeia or , in absence of a monograph, a scientific Latin name (botanical scientific name...) followed by the Homeopathic name*

*** Only one name for each substance should be given in the following order of priority: INN, European Pharmacopoeia, the Romanian Pharmacopoeia, Common name, scientific name*

2.6.5 List of materials of animal and/or human origin contained or used in the manufacturing process of the homeopathic medicinal product

NONE ☐

Name	Function* HSA EX R (state nr.)	Animal origin susceptible to TSE**	Other animal origin	Human origin	Certificate of suitability for EST
1.	❍ ❍ ❍	❍	❍	❍	❍
2.	❍ ❍ ❍	❍	❍	❍	❍
3.	❍ ❍ ❍	❍	❍	❍	❍
4.	❍ ❍ ❍	❍	❍	❍	❍
etc.					

* HAS= homeopathic active substance; EX=excipient (including starting materials used in the manufacture of the active substance/excipient) R=reagent/culture medium (including those used in the preparation of master and working cell banks)

** EST= transmissible spongiform encephalopathy

☐ If a European Pharmacopoeia Certificate of Suitability for TSE is available according to Article Resolution AP/CSP (99)4 of the Council of Europe, please attach in Annex 4.12

3 OTHER MARKETING AUTHORISATION APPLICATIONS

3.1 <u>FOR NATIONAL APPLICATIONS ONLY, PLEASE COMPLETE THE SECTION BELOW, UNDER ARTICLE 702, m)-o) OF LAW NO. 95/2006 ON HEALTHCARE REFORM, TITLE XVII, THE MEDICINAL PRODUCT:</u>

3.1.1 There is/are other Member State(s) where an application for the same* product is pending:

❍YES ❍NO

If YES, please complete Section 3.2.

3.1.2 There is/are other Member State(s) where an authorisation/registration is granted for the same medicinal product*:

❍YES ❍ NO

If YES, please complete Section 3.2 and provide copy.

There are differences which have therapeutic implications between this application and the applications/authorisations for the same product in other Member States (for national applications, under Article 722 and 723 of Law no.95/2006 on healthcare reform, Title XVII, The Medicinal Product).

❍YES ❍NO

If YES, please give:

3.1.3 There is another Member State(s) where an authorisation/registration has been refused/suspended/ revoked by competent authorities for the same* product

❍YES ❍NO

If YES, please complete Section 3.2

**Note: 'same product' means same qualitative and quantitative composition in active substance(s) and having the same pharmaceutical form from applications belonging to the same mother company or group of companies OR which are 'licensees'.*

3.2. Marketing authorisation/registration applications for the same homeopathic medicinal product in the EEA (*('same product' means same qualitative and quantitative composition in active substance(s)and having the same pharmaceutical form from applications belonging to the same mother company or group of companies OR which are 'licensees'.)*

Note: Please refer to Commission Communication 98/C229/03

☐ Countries which have authorised the medicinal product

Country:
Date of authorisation (*yyyy-mm-dd*):
Invented name:
Authorisation number:

☐ Please attach copy of marketing authorisation/registration (Annex 4.15)

☐ Countries in which authorisation of the medicinal product is pending

Country:
Date of submission (*yyyy-mm-dd*):

☐ Countries in which authorisation of the medicinal product has been refused

Country:
Date of refusal (*yyyy-mm-dd*):

☐ Countries in which authorisation of the medicinal product has been withdrawn (by the Applicant before authorisation)

Country:
Date of withdrawal (*yyyy-mm-dd*):
Invented name:
Reason for withdrawal:

☐ Countries in which authorisation of the medicinal product has been withdrawn (by the Applicant after authorisation)

Country:
Date of withdrawal (*yyyy-mm-dd*):
Authorisation number:
Invented name:
Reason for withdrawal:

☐ Countries whose competent authorities have suspended /revoked authorisation of the medicinal product

Country:
Date of suspension/revocation (*yyyy-mm-dd*):
Reason for suspension/revocation:
Invented name:

3.3 For multiple applications of the same homeopathic medicinal product:

Multiple applications for:
Name of the other product(s):
Date of submission (*yyyy-mm-dd*):
Applicant(S):

3.4. Marketing authorisation/registration applications for the same homeopathic medicinal product, outside the EEA (i.e. from applicants belonging to the same mother company or group of companies OR which are "licensees".)

Note: Please refer to Commission Communication 98/C229/03

☐ Countries which have authorised the medicinal product

Country:
Date of authorisation (*yyyy-mm-dd*):
Invented name:
Authorisation number:

☐ Countries in which authorisation of the medicinal product is pending

Country:
Date of submission (*yyyy-mm-dd*):

☐ Countries in which authorisation of the medicinal product has been refused

Country:
Date of refusal (*yyyy-mm-dd*):

☐ Countries in which authorisation of the medicinal product has been withdrawn (by the Applicant before authorisation)

Country:
Date of withdrawal (*yyyy-mm-dd*):
Invented name:
Reason for withdrawal:

☐ Countries in which authorisation of the medicinal product has been withdrawn (by the Applicant after authorisation)

Country:
Date of withdrawal (*yyyy-mm-dd)*
Authorisation number:
Invented name:
Reason for withdrawal:

☐ Countries whose competent authorities have suspended /revoked authorisation of the medicinal product

Country:
Date of suspension/revocation (*yyyy-mm-dd*):
Reason for suspension/revocation:
Invented name:

4. ANNEXED DOCUMENTS (WHERE APPLICABLE)

☐ **4.1** Proof of payment

☐ **4.2** Consent of the Marketing Authorisation Holder for the reference medicinal product who allows an applicant to make use of the pharmaceutical, preclinical and clinical documentation contained in the file on the medicinal product, with a view to examining subsequent applications (for informed consent marketing authorisation applications)

☐ **4.3** Proof of establishment of the applicant in the EEA

☐ **4.4** Letter of authorisation for communication on behalf of the applicant/marketing authorisation holder

☐ **4.5** Curriculum Vitae of the Qualified Person for Pharmacovigilance

☐ **4.6** Manufacturing Authorisation required under Article Article 748 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product (or equivalent, outside of the EEA where MRA or other Community arrangements apply). A reference to EudraGMP will suffice when available.

☐ **4.7** Justification for more than one manufacturer responsible for batch release in the EEA

☐ **4.8** Flow-chart indicating all sites involved in the manufacturing process of the medicinal product or active substance (including sites involved in sampling and testing for batch release of products manufactured in third countries). ALL manufacturing and control sites mentioned throughout the whole dossier MUST be consistent regarding their names, detailed addresses and activities.

☐ **4.9** Statement (or GMP Certificate issued by an EEA inspectorate, when available) from the competent authority which carried out the inspection of the manufacturing site(s)/(not older than 3 years). References to EudraGMP will suffice when available. Where applicable a summary of other GMP inspections performed in the last 2 years.

☐ **4.10** Letter(s) of access to Active Substance Master File(s) or copy of European Pharmacopoeia Certificate(s) of suitability

☐ **4.11** Copy of written confirmation from the manufacturer of the active substance to inform the applicant in case of modification of the manufacturing process or specifications according to Annex I to order of the ministry of health on approval of ”Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products” (transposing Annex I of Directive 2001/83)

☐ 4**.12** European Pharmacopoeia Certificate(s) of suitability for TSE

☐ **4.13** Written consent(s) of the competent authorities regarding genetically modified organisms release in the environment

☐ **4.14** Scientific advice given by CHMP.

☐ **4.15** Copy(ies) of Marketing Authorization(s) granted in an EEA country or third country under Article 702, m)-o) of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product and the equivalent in third countries on request (photocopies of the pages which give the Marketing authorisation number, Date of authorisation and pages which have been signed by the competent authorities).

☐ **4.16** Correspondence with European Commission regarding multiple applications.

☐ **4.17** List of Mock-ups or Samples/specimens sent with the application, as appropriate.

☐ **4.18** List of proposed (invented) names and marketing authorisation holders in the concerned member states.

☐ **4.19** Copy of EMEA certificate for a Vaccine Antigen Master File (VAMF)

☐ **4.20** Copy of EMEA certificate for Plasma Master File (PMF)

☐ **4.21** For each active substance, attach a declaration from the Qualified Person of the manufacturing authorisation holder authorisation holder of each of the manufacturing authorisation holders (i.e. located in EEA listed in Section 2.5.2 where the active substance is used as a starting material that the active substance manufacturer(s) referred to in Section 2.5.3 operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. This does not apply to Blood or blood components

ANNEX No. 3

APPLICATION FOR RENEWAL OF A MARKETING AUTHORISATION FOR MEDICINAL PRODUCTS FOR HUMAN USE

Invented name: Active substance (s): Pharmacotherapeutic classification (Group + ATC code): Pharmaceutical form and strength[1]: Route of administration[1:] Target species [1]: MA number[1]:	Name and address of MA holder: Name and address of Contact Person[2]: Telephone: Fax: E-mail: Applicant's reference:

1- For centrally authorised products, the above information, including container and pack size(s), should be provided as a table in a separate appendix (according to CPMP opinion)

2- As specified in Section 2.4.3 din part 1A of the dossier. If different, attach letter of authorisation.

Signature _____Date _____

Member State/EMEA _____Contact _____

Date of first authorisation in Reference Member State/Community: Date of expiry of current authorisation in Reference Member State/Community:	Date of first authorisation in Romania: Date of expiry of current authorisation in Romania:

APPROVED MANUFACTURERS

Authorised manufacturer(s) (or importer) responsible for batch release in Romania or EEA (according to Articles 748 and 760 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product)

Name:
Address:
Country:
Telephone: *Telefax:* *E-mail:*

Further manufacturers responsible for batch release can be detailed in the text field below, in the same format as shown above

***For blood products and vaccines**:*
State laboratory or laboratory designated for official batch release, as accordance with Articles 823 (1), 825, 826 (1) and (2) and 827 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product
Name:
Address:
Country:

Telephone: *Telefax:* *E-mail:*

Further manufacturers responsible for batch release can be detailed in the text field below, in the same format as shown above.

Site(s) in Romania or the EEA, where batch control/testing takes place, as required by Article 760 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, if different from above:

Name:
Address:
Country:
Telephone: *Telefax:* *E-mail:*

Further sites can be detailed in the text field below, in the same format as shown above.

*Manufacturer(s) of **the medicinal product** and site(s) of manufacture (including diluent and solvent manufacturing sites):*

Name:
Address:
Country:
Telephone: *Telefax:* *E-mail:*

Brief description of functions performed by manufacturer of dosage form/assembler etc.:

Further manufacturers can be detailed in the text field below, in the same format as shown above

*Manufacturer(s) of **the active substance(s)***
Note: All manufacturing sites involved in the manufacturing process of each source of active substance should be listed. Broker or supplier details alone are not sufficient.

Name:
Address:

Country:
Telephone: *Telefax:* *E-mail:*

Further active substance manufacturers can be detailed in the text field below, in the same format as shown above.

QUALITATIVE AND QUANTITATIVE COMPOSITION IN TERMS OF THE ACTIVE SUBSTANCE(S) AND THE EXCIPIENT(S)

(For centrally authorised products the composition should be provided separately in tabular format as part of the Quality Expert Statement).
A note should be given as to which quantity the composition refers (e.g. 1 capsule).
List the active substance(s) separately from the excipients.

*Name of the active substance (s)**	*Quantity*	*Unit*	*Monograph standard*
*Name of excipient (s) **	*Quantity*	*Unit*	*Monograph standard*

**Only one name for each substance should be given in the following order of priority: INN, European Pharmacopoeia, The Romanian Pharmacopoeia, common name, scientific name. The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant*

Details of any overages should not be included in the formulation but stated below:
- active substance (s)
- excipient(s)

(*If revised product information (SPC, Labelling and/or Package Leaflet) is proposed to take account of issues raised by the expert, specify the precise present and proposed wording, underlining or highlighting the changed words. Alternatively, such listing may be provided as a separate document attached to the application form*.)

PRESENT PRODUCT INFORMATION TEXT	**PROPOSED PRODUCT INFORMATION TEXT**

DOCUMENTS APPENDED TO THIS APPLICATION

For applications under NATIONAL procedure:

Module 1:

1.0 Cover letter

1.1 Comprehensive table of content

1.2 Renewal Application Form with the following annexes:

• A list of all authorised product presentations for which renewal is sought in tabular format

• Details on contact persons

• Qualified person in Romania and the EEA for Pharmacovigilance

• Contact person in Romania and the EEA with overall responsibility for product defects and recalls

• Contact person for scientific service in Romania and the EEA in charge of information about the medicinal product

• List of EU Member States / Norway / Iceland where the product is on the market and indicating for each country which presentations are marketed and the launch date

• Chronological list of all post-authorisation submissions since grant of the Marketing authorisation or last renewal: a list of all approved or pending Type IA/IB and Type II variations, Extensions, Notifications under Article 771 (3) of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product; USR, giving the procedure number (where applicable), date of submission, date of approval (if approved) and brief description of the change

• Chronological list of letters related to Follow-up measures

• A statement, or when available, a certificate of GMP compliance, not more than three years old, for the manufacturer(s) of the medicinal product listed in the application issued by an EEA competent authority or MRA partner authority. A reference to the Community EudraGMP database will suffice, once this is available.

• For manufacturing sites of the medicinal product not located in the EEA or in the territory of an MRA partner, a list of the most recent GMP inspections carried out by other authorities indicating the date, inspection team and outcomes

• In accord with Article 754, (f) of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, the manufacturing authorisation holder must use as raw materials only such active substance(s) as manufactured in accordance with the guidelines on good manufacturing practice for starting materials as adopted by the Community.

The following declarations are required:

i. A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders (i.e. located in the EEA), listed in the application form where the active substance(s) is used as a starting material

ii. Where different, a declaration by the Qualified Person of the manufacturing authorisation holder(s) listed in the application form as responsible for batch release.

1.3 Product information:

1.3.1 SPC, Labelling and Package Leaflet

Current SPC in English, either accompanied by a translation or not, in case a new SPE is proposed with highlighted proposed changes, in English and the appropriate translation.

1.3.3 Specimen/sample

1.4 Information about the expert's qualification and experience

1.4.1 For quality documents (signature + CV)
1.4.3 For clinical documents(signature + CV)

Module 2:

2.3 Quality Overall Summary (Quality Expert Statement)
2.5 Clinical Overview (Clinical Expert Statement)

Module 5:

5.3.6 Reports of Post-marketing experience (Periodic Safety Update Report and Summary Bridging Report if applicable)

For medicinal products for human use authorized in Romania under <u>CADREAC</u> simplified procedure for medicinal products authorised in the EU under centralised procedure or mutual recognition procedure:

Module 1:

1.0 Cover letter
1.1 Comprehensive table of content
1.2 Renewal Application Form with the following annexes

• A list of all authorised product presentations for which renewal is sought in tabular format (according to Annex structure of CHMP Opinion)

• Details on contact persons

• Qualified person in Romania and the EEA for Pharmacovigilance

• Contact person in Romania and the EEA with overall responsibility for product defects and recalls

• Contact person for scientific service in Romania and the EEA in charge of information about the medicinal product

• List of EU Member States / Norway / Iceland where the product is on the market and indicating for each country which presentations are marketed and the launch date

• Chronological list of all post-authorisation submissions since grant of the Marketing authorisation or last renewal: a list of all approved or pending Type IA/IB and Type II variations, Extensions, Notifications under Article 771 (3) of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product; USR, giving the procedure number (where applicable), date of submission, date of approval (if approved) and brief description of the change

• Chronological list of Follow-up measures and any Specific Obligations submitted since grant of marketing authorisation or last renewal indicating scope, status, date of submission and date when issue has been resolved

• Revised list of all remaining Follow-up measures/post-authorisation commitments, and for Community Authorisations only any Specific Obligations and signed letter of commitment (where applicable)

• A statement, or when available, a certificate of GMP compliance, not more than three years old, for the manufacturer(s) of the medicinal product listed in the application issued by an EEA competent authority or MRA partner authority. A reference to the Community EudraGMP database will suffice, once this is available.

• in addition, For manufacturing sites of the medicinal product not located in the EEA or in the territory of an MRA partner, a list of the most recent GMP inspections carried out by other authorities indicating the date, inspection team and outcome

• in accord with Article 754 lit. (f) of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, the manufacturing authorisation holder must use as raw materials only such

active substance(s) as manufactured in accordance with the guidelines on good manufacturing practice for starting materials as adopted by the Community.

The following declarations are required:

i. A declaration by the Qualified Person of each of the manufacturing authorisation holders (i.e. located in the EEA), listed in the application form where the active substance(s) is used as a starting material

ii. Where different, a declaration by the Qualified Person of the manufacturing authorisation holder(s) listed in the application form as responsible for batch release.

1.3 Product information:
1.3.1 SPC, Labelling and Package Leaflet
1.3.3 Specimen
1.4 Information about the expert's qualification and experience
1.4.1 For quality documents (signature + CV)
1.4.2 For nonclinical documents (signature + CV) – if applicable
1.4.3 For clinical documents(signature + CV)

Module 2:

2.3 Quality Overall Summary (Quality Expert Statement)
2.4 Nonclinical Overview (Nonclinical Expert Statement), if applicable
2.5 Clinical Overview (Clinical Expert Statement)

Module 5:

5.3.6 Reports of Post-marketing experience (Periodic Safety Update Report and Summary Bridging Report, if applicable)

I hereby make application for the above Marketing Authorisation to be renewed. I declare that the quality of the product, in respect of the methods of preparation and control, has been regularly updated by variation procedure to take account of technical and scientific progress in accordance with Article 728 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product. The product conforms to current CHMP quality guidelines where relevant. I confirm that no changes have been made to the product particulars other than those approved by the Competent Authorities.

Fees will be paid according to NMA payment rules ☐ Amount/Currency:

Main Signatory _____ Function_____

Print name _____ Date

Second Signatory _____ Function_____
(where appropriate)
Print name _____ Date