MINISTRY OF HEALTH

ORDER
on amendment of the Annex to the Minister of Public Health Order No. 895/2006 on approval of the Regulations regarding marketing authorisation and surveillance of medicinal products for human use

On seeing the approval report of the Direction on drug policy Cs. A. No. 12.388 of 24 November 2010,

Taking into account:

- the provisions of Title XVII „The Medicinal Products" of Law No. 95/2006 on healthcare reform, as amended;

- Government Decision No. 734/2010 related to the set up and functioning of the National Agency for Medicines and Medical Devices,

based on Government Decision No. 144/2010 on the organisation and functioning of the Ministry of Health, as amended,

the minister of health hereby issues the following order:

Article I. – The Annex to the Minister of Public Health Order No. 895/2006 on approval of the Regulations regarding marketing authorisation and surveillance of medicinal products for human use, published in the Official Gazette of Romania, Part I, No. 660 of 1 August 2006, is amended and replaced with the Annex, which is integral part of this Order.

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

Minister of health,

Cseke Attila

Bucharest, 24 November 2010.
No. 1.448.

ANNEX
(Annex to Order no. 1448/2010)

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

CHAPTER I
Overview

Article 1. - (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, as amended.

(2) These regulations are applicable in case of applications submitted through national procedure.

(3) Likewise, these Regulations are applicable to medicinal products for human use authorised through the mutual recognition and the decentralized procedure, taking into account the specific information related to the procedures detailed in Chapter IV.

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

Article 3. - The marketing authorisation is granted by the National Agency for Medicines and Medical Devices to medicinal products for human use that meet quality, safety and efficacy requirements provided in Article 702 of Law 95/2006, as amended.

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

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 site 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 European Community).

Article 6. – The National Agency for Medicines and Medical Devices 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 Agency for Medicines and Medical Devices may require external experts for assessment 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 Agency for Medicines and Medical Devices an application in the form shown in Annex 1.

(2) The application for marketing authorisation shall be submitted together with documents and information mentioned under Article 702 (4) and (5) of Law 95/2006 and as outlined in the Annex to Order of the Minister of Public Health No. 906/2006 for approval of analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products, as amended (transposing Directive 2003/63/EC of 25 June 2003, amending Directive 2001/83/EC of the European Parliament and Council of 6 November 2001, on the Community code relating to medicinal products for human use).

(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, as amended.

Article 9. - In line with cu provisions of Title XVII "The Medicinal Product" of Law 95/2006, as amended, 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, as amended (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, as amended ("bibliographic" application for medicinal products with well-established medical use);

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, as amended (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 (2) b) of Law 95/2006, as amended (“combined” 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, as amended (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, as amended (application for a fixed combination);

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

5. Homeopathic medicinal products according to Article 710 of Law 95/2006, as amended; (application for homeopathic medicinal products – the applicant submits to the National Agency for Medicines and Medical Devices 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, as amended, and Module 2 "Summaries" of the Annex to Minister of Public Health Order No. 906/2006, as amended.

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

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), provided in the Annex to the Minister of Public Health Order No. 906/2006, as amended, with objective outline of qualitative and quantitative results;

b) Expose the observations in accordance with the provisions of Module 2 ,,Summaries" in the Annex to the Order of the Minister of Public Health No. 906/2006, as amended;

b) Provide observations in line with provisions of Module 2 "Summaries" of the Annex to Minister of Public Health Order No. 906/2006, as amended;

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, as amended, the assessor 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 material/s, 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 the assessment procedure of the dossier, the National Agency for Medicines and Medical Devices may request the performance of an inspection at the manufacturing site(s), another inspection at the site(s) of performance of preclinical and/or clinical tests and/or another one at the site of the MAH or his/her representative, in view of checking compliance with the requirements and compliance of the pharmacovigilance system by the inspectors of the Pharmaceutical Inspection Department of the National Agency for Medicines and Medical Devices.

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 dossier in view of marketing/renewal authorisation should be forwarded via e-mail or presented in electronic format (CD/DVD), modules I - V, and in written form, signed in original, the authorisation application and the letter attached to the authorisation dossier (single copy only).

(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 Annex to Minister of Public Health Order No. 906/2006, as amended – in the format of the Common Technical Document.

Article 15. - The documentation may be submitted in Romanian, English or French.

Article 16. - (1) The marketing authorisation fee provided under Article 854 of Law 95/2006, as amended, as well as authorisation Tariffs 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 in line with payment norms of the National Agency for Medicines and Medical Devices.

(2) When check of control methods has been necessary, the tariffs for laboratory testing established through decision of the Administration Council of the National Agency for Medicines and Medical Devices, approved through Minister of Health Order 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 assessment procedure.

CHAPTER III
Marketing Authorisation Procedure

Article 17. - Applicants submit to the Data and document management, the Registry – document distribution and release Bureau of the Information Logistics and Electronic Management of Data Department, 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 Registry – document distribution and release Bureau 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. - (1) After payment of the authorisation tax and tariff and confirmation by the Economic Department of payment as stipulated under Article 16 (1), the Data and document management service forwards the authorisation application and dossier to the Administrative Verification and Product Index Bureau and to the National Procedure Administrative service of the National Procedure Department, in view of validation within 30 days.

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 is distributed to assessment services.

(2) If the submitted dossier is available, it is distributed to the assessment services of the National Procedure Department, the European Procedure Department or, for biological products, to the Biological Product Assessment and Control Department.

(3) If, throughout the validation stage of the dossier, it is discovered that it must be supplemented with several administrative and technical documents/information which have not been identified on the date of application submission, the list containing the requirements needed in view of the validation of the authorisation dossier shall be granted.

(4) The authorisation dossier forwarded to the National Agency for Medicines and Medical Devices is considered validated only after the receipt of all required documents and after their assessment.

(5) The applicant shall be informed that the application has been validated from an administrative viewpoint and thus enters the 210-day period stipulated in Article 722 of Law No. 95/2006, as amended, in view of assessment of the documentation concerning the release of the marketing authorisation.

Article 21. - The National Procedure Department, the European Procedure Department or, for biological products, the Biological Product Assessment and Control Department examines whether the documentation submitted is compliant with provisions of Articles 702, 703, 704, 705, 706 and 707 of Law 95/2006, as amended, and whether all the conditions for granting a marketing authorisation are satisfied.

Article 22. - Should the submitted dossier be incomplete, the time mentioned under Article 20 (5) is suspended before additional information is provided by the applicant as requested by the National Agency for Medicines and Medical Devices.

Article 23. - The process involving assessment of the authorisation dossier 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 (3), control departments of the National Agency for Medicines and Medical Devices check the control methodology outlined in the documentation; in case of deficiencies or 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. The period stipulated in Article 20 (5) is suspended until the assessor/marketing authorisation committee provides the outcomes and conclusions related to control methodology.

(2) Exception to this provision is the 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 in maximum 60 days as of their submission.

Article 25. - After issuance, complete assessment 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. – After the expression of a favourable opinion by the Commission for marketing authorisation and confirmation granted by the Economic Department related to the payment of amounts related to authorisation procedure, in accordance with Article 16 (1) and (2), the marketing authorisation and the 5 annexes are set up by the Registry – document distribution and release Bureau from the Information Logistics and Electronic Management of Data Department and by the Medical Information Bureau from the National Procedure 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:

a) marketing authorisation number;

b) year of authorisation;

c) number corresponding to authorised types of packaging.

Article 29. - In the case of influenza vaccine, documentation shall be yearly updated in line with the 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. – As stipulated in Article 730 (10) of Law No. 95/2006 on healthcare reform, as amended, the dossier remains in the possession of the National Agency for Medicines and Medical Devices and is recorded by the Archive Service of the General Administration Department. In circumstances such as provided under Article 730 (10) of Law 95/2006 on healthcare reform, as amended, documentation is returned on applicant request.

CHAPTER IV
Marketing authorisation of medicinal products authorised through mutual recognition, or decentralised procedures

Article 31. - (1) In case of marketing authorisation applications sent through mutual recognition/decentralised procedure, the specific provisions stipulated in section 5, Title XVII – The medicinal product of Law No. 95/2006, as amended, the NAMMD guidelines on the handling of marketing authorisation applications through mutual recognition and decentralised procedure, as well as the guidelines of the Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human, CMD(h) are applied; these can be accessed online, on the website of the "Heads of Medicines Agencies": http://www.hma.eu.

(2) Information on the manner of display of the dossier and samples, of the number of copies of each CTD module (Common Technical Document) can be found in Chapter 7 of Volume 2A Notice to Applicants, published on the website of the European Commission - www.ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev 1.htm.

CHAPTER V
Rejection of marketing authorisation

Article 32. - The National Agency for Medicines and Medical Devices may reject marketing authorisation for a medicinal product, in line with provisions of Article 732 of Law 95/2006, as amended.

Article 33. - In the case of an unfavourable opinion of the Marketing Authorisation Commission of the National Agency for Medicines and Medical Devices, the applicant is notified in writing on rejection of marketing authorisation; the decision for rejection is accompanied by a report justifying the decision based on conclusions of assessment reports.

Article 34. - Within 30 days as of receipt of the rejection report, the applicant may send the National Agency for Medicines and Medical Devices 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 Agency for Medicines and Medical Devices must respond on its resolution of the appeal; the solution may be disputed and subjected to administrative law.

CHAPTER VI
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, as amended, the application for marketing authorisation renewal is submitted to the National Agency for Medicines and Medical Devices 6 months prior to expiry of previous authorisation.

(2) The applicant submits an application for marketing authorisation renewal to the National Agency for Medicines and Medical Devices, 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, namely the Periodic Safety Update Report (PSUR) is submitted to the National Agency for Medicines and Medical Devices.

(4) The applicant shall present the documents mentioned in the application for marketing authorisation renewal.

Article 38. - (1) The steps of the renewal procedure of the authorisation are the same as those mentioned in Chapter III. The assessment of the dossier submitted by the applicant for the renewal of the marketing authorisation is assessed by the National Procedure Department and, for biological medicinal products, by the Biological Product Assessment and Control Department, except for pharmacovigilance data (PSURs) for synthesis products authorised through national procedure, assessed by the European Procedure Department.

Stages of the procedure for marketing authorisation renewal are the same as those 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, as amended, 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 the enforcement of the previsions mentioned in Article 728 of Law 95/2006, as amended.

(4) Once renewed, based on the provisions of Article 730 (5) of law No. 95/2006, as amended, the marketing authorisation is available for an unlimited period, except for the circumstances stipulated by the Law.

CHAPTER VII
Marketing authorisation suspension and withdrawal

Article 39. - In case of risk to public health, the National Agency for Medicines and Medical Devices 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, as amended, the National Agency for Medicines and Medical Devices shall suspend, withdraw or amend 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, as amended, are incorrect or have not been amended in accordance with Article 29;

f) Controls carried out on the medicinal product and/or on its ingredients and 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, as amended;

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

(2) Discontinuation ceases when the issues underlying the respective decision have been solved, and the marketing authorisation commission decides upon the cancellation of the imposed measure.

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 communication to the Ministry of Health and, on a case-by-case basis, to the National Health Insurance House of the NAMMD decision on the change, cancellation or withdrawal of the marketing authorisation, this shall equally be communicated to the Marketing Authorisation Holder.

CHAPTER VIII
Surveillance of medicinal products for human use

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

a) Check up the distribution chain via the inspection activity of the Pharmaceutical Inspection Department in view of assessing the quality of medicinal products which have been authorised for marketing in Romania

(sampling and control of local samples, settlement of complaints, rapid alerts etc.);

b) 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;

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

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

e) Take part in the settlement of certain notifications related to the potential existence of certain counterfeited medicinal products.

(2) For immunological products and products derived from human blood/plasma imported from EU Member States, pending marketing in Romania after authorisation, Marketing Authorisation Holders are requested to submit to the National Agency for Medicines and Medical Devices the compliance certificate for the imported batch, issued by the control authority of the respective Member State.

(3) For immunological products and products derived from human blood/plasma for which the official batch release has been performed by a control authority in a EU Member State, the National Agency for Medicines and Medical Devices approves the marketing of the respective biological product on Romanian territory, exclusively based upon the compliance certificate issued by the respective control authority.

(4) The National Agency for Medicines and Medical Devices performs the official batch release in view of marketing of immunological products and products derived from human blood/plasma in Romania, from import (coming from third countries) and EU Member States, whose batches haven't been officially released in the EU, due to various reasons. In such cases, the MAH shall submit to the National Agency for Medicines and Medical Devices the following:

a) relevant samples for the batch to be marketing in Romania, in view of laboratory testing;

b) the summary of the batch protocol;

c) a copy of the compliance certificate issued by the manufacturer.

Article 44. - Annexes 1 - 3 are integral parts of these Regulations.

ANNEX 1
to Regulations

APPLICATION FOR MARKETING AUTHORISATION OF MEDICINAL PRODUCTS FOR HUMAN USE

SUMMARY OF THE DOSSIER

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APPLICATION FOR MARKTING AUTHORISATION: ADMINISTRATIVE DATA

The application form is to be used for an application for a marketing authorisation of a medicinal product for human use, submitted to:

a) The European Medicines Agency through centralised procedure; or

b) The National Agency for Medicines and Medical Devices, through national/mutual recognition/decentralised procedure.

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

For the centralised procedure, a mixed application is allowed (Where deemed necessary, information shall be successively provided for each pharmaceutical form and strength).

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 Agency for Medicines and Medical Devices, during the authorisation procedure**:**

It is hereby confirmed that all existing data relevant to the quality, safety and efficacy of the medicinal product for human use have been supplied in the dossier, according to the rules.

It is hereby confirmed that the fees and tariffs shall be paid in accordance with the Norms established by the National Agency for Medicines and Medical Devices **.

On behalf of the applicant:

……..

Signature: ……

Name *

……

Function

……..…….. …….

Place Date (year, month, day)

- Please attach the letter of authorisation issued by the applicant for the person responsible for communication with the National Agency for Medicines and Medical Devices/signature right on behalf of the applicant, in Annex 6.4.
- Please attach letter of authorisation for communication with NMA/signing on behalf of the applicant.

** If taxes have been paid, please attach the proof in Annex 6.1 – see information on payment in the Notice *to Applicants*, Volume 2 A, chapter 7.

Summary

Declaration and signature

1. Type of application

1.1. This application concerns:

1.2. Designation as orphan medicinal product

1.3. Application for change of an existing marketing authorisation referring to Order of the Minister of Public Health No. 874/2006 on approval of the Norms on the administrative procedure of the National Agency for Medicines and Medical Devices on handling variations.

1.4. The application for marketing authorisation is submitted in accordance with Law No. 95/2006 on healthcare reform, as amended, Title XVII – The medicinal product.

1.5. The application for marketing authorisation is submitted in accordance with Article 704 (1), Article 704 (5), Article 727 and 785 of Law No. 95/2006, as amended, Title XVII – The medicinal product and with Article 14 (7)-(9) of Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and surveillance of medicinal products for human and veterinary use and establishing an European Medicines Agency.

2. Particularities of the application for marketing authorisation of a medicinal product for human use

2.1. ATC code(s) and name(s)

2.2. Pharmaceutical form, strength, route of administration, container and package size

2.3 Legal status

2.4. Marketing Authorisation Holder/Contact person/Company

2.5. Manufacturers
2.6. Qualitative and quantitative composition
3. Scientific counselling
4. Paediatric development programme
5. Other marketing authorisation applications
6. Documents attached to the application (where required)

1. Type of application

NOTE:

The following sections should be completed where appropriate.

1.1. This application concerns:

❍ 1.1.1. <u>The centralised procedure</u> (in accordance with Regulation (EC) No. 726/2004

❍ YES ❍ NO

❍ „Mandatory field of application" [Article 3 (1)]

❍ Annex 1 (Biotechnology products)

❍ Annex 3 (New active substance for mandatory indications) Date of approval by the Committee for Medicinal Products for Human Use (*CHMP*): (yyyy-mm-dd)

❍ Annex 4 (Medicinal product designed as orphan)

❍ „Optional field of application" [Article 3 (2)]

❍ Article 3 (2) a) (New active substance) Date of approval by the CHMP:

❍ Article 3 (2) b) (Substantial innovation or interest of the patients at Community level) (yyyy-mm-dd)

❍ „Generic medicinal product of a medicinal product authorised through centralised procedure" [Article 3 (3)]

❍ Rapporteur: (Name of CHMP member) ❍ CoRapporteur: (Name of CHMP member)

❍ 1.1.2. Mutual Recognition Procedure [in accordance with Article 736 (2) of Law No. 95/2006, as amended, Title XVII – The medicinal product]

❍ 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)

❍ First use

- Concerned Member State(s):

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

Common date proposed for renewal:

Specify whether a waiver/change occurred in the cycle of the Periodic Safety Update Report (PSUR), in view of harmonisation with the substance birthdate.

❍ „Repeat use" first wave (Also fill in section 5.2.)

- Interested Member State(s):

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

Please copy the boxes above for subsequent the following procedures.

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

Common date agreed for renewal:

❍ 1.1.3. <u>Decentralised procedure</u> [in accordance with Article 736 (3) of Law No. 95/2006, as amended, Title XVII „The medicinal product"

❍ YES ❍ NO

- Reference Member State:
- Procedure number:
- Interested Member State(s):

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

▪ Specify whether an exemption to/change of the PSUR cycle has been requested in view of harmonisation with the substance birthdate.

❍ 1.1.4. National procedure

▪ Member State:

▪ Application number, if available:

▪ Specify whether an exemption to/change of the PSUR cycle has been requested in view of harmonisation with the substance birthdate.

1.2. Information about the orphan medicinal product

1.2.1. This medicinal product has been proposed as an orphan medicinal product:

❍ No

❍ Yes Number of procedure for designation as an orphan medicinal product:

❍ Pending

❍ Designed as orphan medicinal product

Date (yyyy-mm-dd):

Based on the „substantial benefit" criterion: ❍ Yes ❍ No

Number in the Community register of orphan medicinal products:

☐ Please attach the copy of the decision concerning designation as orphan medicinal product (Annex 6.18)

❍ Designation as orphan medicinal product has been refused.

Date (yyyy-mm-dd):

Reference number of Commission decision:

❍ Designation as orphan medicinal product has been refused.

Date (yyyy-mm-dd):

Information concerning marketing exclusivity of orphan medicinal products

Is there other medicinal product designated as orphan for an ailment connected to the indication proposed via this application:

❍ No

❍ Yes

The following designation(s) as orphan medicinal product(s) is (are) specified:

Does any of the orphan medicinal products own a marketing authorisation in the European Union?

❍ No

❍ Yes

Please specify:

▪ Invented name, strength, pharmaceutical form of the authorised medicinal product:……

▪ Marketing Authorisation Holder: …….

▪ Date of authorisation: …….

If YES, the medicinal product for which this application is submitted is considered „similar" to any authorised orphan medicinal product(s) [as stipulated in Article 3 of Regulation (EC) No. 847/2000 of 27 April 2000 laying down the provisions for

implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts ‘similar medicinal product’ and ‘clinical superiority’].

❍ No (fill in module 1.7.1)

❍ Yes (fill in modules 1.7.1 and 1.7.2)

1.3. This is an application for change of an existing marketing authorisation referring to Order of the Minister of Public Health No. 874 /2006, where deemed necessary.

❍ YES (Please fill in the section below, as well as section 1.4.)

❍ NO (Fill in section 1.4. only)

Please specify:

☐ Quality change in the declared active substance, undefined as the new active substance

❍ Replacement with a different salt/ester, mixture/by-product (of the same therapeutic entity)

❍ Replacement with a different isomer, isomer mixture, isolated isomer mixture

❍ Replacement of a biological substance or of a biotechnology product

❍ new ligands or coupling devices for radiopharmaceuticals

❍ change of the extraction diluent or of the balance between the herbal medicinal product and the herbal preparation

☐ change of bioavailability

☐ change of pharmacokinetics

☐ change/addition of a new strength/activity

☐ change/addition of a new pharmaceutical form

☐ change/addition of a new manner of administration

NOTE:

The applicant of this marketing authorisation application should be the same as the already existing MAH.

This section should be filled in without being detrimental to the provisions of Article 702 (3), Article 704 (1), Article 705, 706, 707 and 726 of Law No. 95/2006, as amended, Title XVII – The medicinal product.

● For marketing authorisations in the European Union/Romania:

- Name of the Marketing Authorisation Holder;
- Invented name, strength and pharmaceutical form of the existing product;
- Authorisation number(s).

1.4. A marketing authorisation submitted in accordance with the following articles of Law No. 95/2006, as amended, Title XVII – The medicinal product.

NOTE:

This section must be filled in for any type of application for marketing authorisation, including the applications mentioned in section 1.3.

For further details, please consult the Notice to Applicants, Volume 2A, Chapter 1.

1.4.1. ❍ Article 702 (4) of Law No. 95/2006, as amended, Title XVII – The medicinal product (full dossier containing administrative, preclinical and clinical data on quality*)

❍ New active substance

NOTE:

Compound of a product still unauthorised by a competent authority or in the European Community (for the centralised procedure)

❍ Known active substance

NOTE:

Compound of a product already authorised by a competent authority or in the European Community

- The Marketing Authorisation Holder is the same or differs.

1.4.2. ❍ Article 704 (1) and (2) of Law No. 95/2006, as amended, Title XVII – The medicinal product – marketing authorisation application for generic medicinal products

NOTE:

Application for generic medicinal products, as defined in Article 704 (2) b) referring to the so-called reference medicinal products authorised for marketing in a Member State or in the European Community.

- Complete administrative and quality information, corresponding clinical And preclinical information, when required.

- See Notice to Applicants, Volume 2A, Chapter 1.

■ Reference medicinal product which is or was authorised for less than 6/10 years in the European Economic Area *(EEA):*

▪ Name of the product, strength and pharmaceutical form:

▪ Marketing Authorisation Holder:

▪ First authorisation: date (yyyy-mm-dd) Member State (EEA)/European Community:

■ Reference Medicinal Product authorised in the European Union/Romania:

▪ Product name, strength and pharmaceutical form:

▪ Marketing Authorisation Holder:

▪ Authorisation number(s):

■ Medicinal products used in bioequivalence studies, where deemed necessary:

▪ Name of the product, strength and pharmaceutical form:

▪ Marketing Authorisation Holder:

▪ Reference Member State which purchased the reference product:

1.4.3. ❍ Article 704 (3) of Law No. 95/2006, as amended, Title XVII – The medicinal product – „hybrid”(mixed) application

NOTE:

An application for marketing authorisation of a medicinal product referring to a so-called reference medicinal product authorised for marketing in a Member State or in the European Community (e.g. different pharmaceutical form, different therapeutic indications)

- Complete administrative and quality information, preclinical and clinical data in accordance with the regulations (Notice to Applicants, Volume 2A, Chapter 1)

■ Reference medicinal product which is or was authorised for less than 6/10 years in the European Economic Area *(EEA):*

▪ Name of the product, strength and pharmaceutical form:

▪ Marketing Authorisation Holder:

▪ First authorisation: date (yyyy-mm-dd) Member State (EEA)/European Community:

■ Reference Medicinal Product authorised in the European Union/Romania:

▪ Name of the product, strength and pharmaceutical form:

▪ Marketing Authorisation Holder:

▪ Authorisation number(s):

- * For extensions of complete marketing authorisation applications, reference can only be made to preclinical and clinical data.

■ Medicinal products used in bioequivalence studies, where required

▪ Name of the product, strength and pharmaceutical form:

▪ Marketing Authorisation Holder:

▪ Member State from where the reference medicinal product has been purchased:

■ Differences occurred after comparing the product with the original product:

☐ Changes in the active substance(s)

☐ Changes in therapeutic indications

☐ Changes in pharmaceutical form

☐ Change in strength (changes in amount of active substance(s))

☐ Change in route of administration

☐ Bioequivalence cannot be proved through bioavailability studies

1.4.4. ❍ Article 704 (4) of Law No. 95/2006, as amended, Title XVII – The medicinal product – application for authorisation of similar biological products

NOTE:

Application for authorisation of a product concerning a reference biological product

Complete administrative and quality information, preclinical and clinical information in accordance with the regulations (Notice to Applicants, Volume 2A, Chapter 1)

■ Reference medicinal product which is or was authorised for less than 6/10 years in the European Economic Area *(EEA):*

▪ Name of the product, strength and pharmaceutical form:

▪ Marketing Authorisation Holder:

▪ First authorisation: date (yyyy-mm-dd) Member State (EEA)/European Community:

■ Reference Medicinal Product authorised in the European Union/Romania:

▪ Name of the product, strength and pharmaceutical form:

▪ Marketing Authorisation Holder:

▪ Marketing authorisation number(s):

■ Medicinal product used in bioequivalence studies, where required

▪ Name of the product, strength and pharmaceutical form:

▪ Marketing Authorisation Holder:

▪ Member State from where the reference medicinal product has been purchased:

1.4.5. ❍ Article 705 of Law No. 95/2006, as amended, Title XVII – The medicinal product – for medicinal products having a well-established use (bibliographic application)

NOTE:
For further details please consult the Notice to Applicants, Volume 2A, Chapter 1.
Only preclinical and clinical data can be mentioned for the applications in view of bibliographic extensions.

1.4.6. ❍ Article 706 of Law No. 95/2006, as amended, Title XVII – The medicinal product – application for authorisation of a fixed combination

NOTE:
Complete administrative and quality information, preclinical and clinical information only for combinations.
Only preclinical and clinical data can be mentioned for line extension applications for fix combinations.

1.4.7. ❍ Article 707 of Law No. 95/2006, as amended, Title XVII – The medicinal product – informed consent application

NOTE:
Marketing Authorisation Application for a product having the same qualitative and quantitative composition in terms of the active substance and the same pharmaceutical form as an authorised product whose MAH consented to the use of the respective information in view of supporting this application.
Complete administrative data is submitted in accordance with the pharmaceutical, clinical and preclinical information.
The authorised product and the marketing authorisation application may have the same/different Marketing Authorisation Holder.

Product authorised in the European Union/Romania:

- Name of the product, strength and pharmaceutical form:
- Marketing Authorisation Holder:
    - Marketing Authorisation Number(s):

☐ Please attach the agreement of the MAH of the already authorised product (Annex 6.2).

1.4.8. ❍ Article 714 of Law No. 95/2006, as amended, Title XVII – The medicinal product – application for authorisation of traditional herbal medicinal products"

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

1.5. This application should be taken into account with the following articles of Law No. 95/2006, as amended, Title XVII – The medicinal product or with the articles of Regulation (EC) No. 726/2004

1.5.1. ❍ Conditional approval

NOTE: Only for centralised procedure in accordance with Article 14 (7) of Regulation (EC) No. 726/2004.

1.5.2. ❍ Exceptional circumstances

NOTE:
In accordance with Article 727 of Law No. 95/2006 and Article 14 (8) of Regulation (EC) No. 726/2004.

1.5.3. ❍ Accelerated assessment

NOTE:
Only for centralised procedure in accordance with Article 14 (9) of Regulation (EC) No. 726/2004.
Date of CHMP approval:
(yyyy-mm-dd)

1.5.4. ❍ Article 704 (1) of Law No. 95/2006, as amended (one-year data exclusivity for a new indication)
1.5.5. ❍ Article 704 (5) of Law No. 95/2006, as amended (one-year data exclusivity for a new indication)
1.5.6. ❍ Article 785 of Law No. 95/2006, as amended (one-year data exclusivity for change of classification)

2. Marketing Authorisation Application particulars

2.1. Name/Name 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 6.19.

2.1.2. Name of the active substance(s):
NOTE:
Only one name should be given in the following order of priority: International Non-proprietary 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 SPC Guidelines)] .

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 – 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 packaging, please give:

2.2.3.1. Packaging size:

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. 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. (See Notice to Applicant, Volume 2A, Chapter 7, Annex 6.17)

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, as amended)

❍ 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, as amended.

** 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 healthcare professionals only
❍ Promotion to the general public and healthcare 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 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: ☐ If different from point 2.4.1 above, attach letter of authorisation (Annex 6.4)
Company name:
Address:
Country:
Telephone:
Telefax:
E-mail:

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

Name: ☐ If different from point 2.4.1 above, attach letter of authorisation (Annex 6.4)
Company name:
Address:
Country:
Telephone:
Telefax:
E-mail:

2.4.4. Qualified person in the European Economic Area for Pharmacovigilance

Name:
Company name:
Address:
Country:
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 the European Economic Area as referred to in Article 809 of Law No. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, as amended

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

2.5. Manufacturers

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

2.5.1. Authorised manufacturer(s) (or importer) responsible for batch release in the European Economic Area in accordance with Articles 748 and 760 of Law No. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, as amended:

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 (OMCL), where the official batch release takes place (in accordance with Articles 823 (1), 825, 826 (1) and (2) and 827 of Law No. 95/2006, Title XVII, The Medicinal Product, as amended, 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, as amended

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 a 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, as amended):

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 a copy of the Manufacturing Authorisation 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 the 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 the inspection report 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:

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

☐ For each active substance, a statement of the qualified person of the MAH(s) mentioned in section 2.5.1 and a statement of the qualified person of the MAH(s) mentioned in
section 2.5.2 shall be submitted, where the active substance is used as a starting material, attesting the fact that the manufacturer(s) of active substance mentioned in section 2.5.3 operate in accordance with the Good Manufacturing Practice rules for active substances.

• 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 a copy of the certificate in Annex 6.10.

• Is there any standard dossier of the European product (European Drug Master File - *EDMF*) for the reference/original active substance(s)

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 the European Medicines Agency (EMA)/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 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2011 on the Community code relating to medicinal products for human use, 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 6.20

(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 shall be included 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:
E-mail:
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 the 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 (for further details, please consult the SPC Guideline)

Details of any overdose 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*			Animal origin susceptible to TSE**	Other animal origin	Human origin	Certificate of suitability for EST (state number)
	AS	EX	R				
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 6.21

* 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 for human use 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 of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms (GMOs) and repealing Council Directive 90/220/EEC?

❍ YES ❍ NO

☐ Please attach a copy of the written consent 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:
Data (yyyy-mm-dd):
Reference:

☐ 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. Please fill in the section below for the applications authorised through national procedure, in accordance with Article 702 (4) m)-o) of Law No. 95/2006, as amended, Title XVII - The medicinal product:

5.1.1. Is (are) there any Member State(s) where an application for authorisation for the same product has been submitted

❍ YES ❍ NO

If YES, Section 5.2 must be completed

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, as amended, 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 same 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

☐ Countries which have authorised the medicinal product:
Country:
Date of authorisation (yyyy-mm-dd):
Invented name:
Authorisation number:
☐ Please provide copy of the marketing authorisation (Annex 6.15)
☐ 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:
Grounds 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:
Grounds for withdrawal:
☐ Countries whose competent authorities have suspended/revoked authorisation of the medicinal product
Country:
Date of suspension/revocation (yyyy-mm-dd):
Grounds for suspension/revocation:
Invented name:

5.3. Multiple applications for marketing authorisation for the same product:
Multiple applications for marketing authorisation:
Name of the other products:
Date of submission of the application(s) (yyyy-mm-dd):
Applicant(s):

☐ Copies of the correspondence with the European Commission are attached in case of the authorisation through centralised procedure (Annex 6.16)

5.4. Marketing authorisation applications for the same 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’.)

☐ Countries which have authorised the medicinal product:
Country:
Date of authorisation (yyyy-mm-dd):
Invented name:
☐ Countries in which an application for authorisation has been submitted
Country:
date of submission of the application (yyyy-mm-dd):
☐ Countries in which authorisation of the medicinal product is pending
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:
Grounds 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:
Grounds for withdrawal:
☐ Countries whose competent authorities have suspended/revoked authorisation of the medicinal product
Country:
Date of suspension/revocation: (yyyy-mm-dd):
Grounds for suspension/revocation:
Invented name:

6. Annexed documents (where applicable)

☐ 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 748 of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, as amended (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 Minister of Health No. 906/2006 on approval of Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products, with further amendments (transposing Annex I of Directive 2001/83/EC)

☐ 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 Authorisation(s) granted in an EEA country or third country under Article 702 (4) 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. Copy of the decision for assignment as orphan medicinal product.

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

☐ 6.20. Copy of EMEA certificate for a Vaccine Antigen Master File (VAMF)

☐ 6.21. Copy of EMEA certificate for Plasma Master File (PMF)

☐ 6.22. 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 2
to Regulations

APPLICATION FOR MARKETING AUTHORISATION
OF HOMEOPATHIC MEDICINAL PRODUCTS FOR HUMAN USE

SUMMARY OF THE DOSSIER

●●●●●

APPLICATION FOR MARKETING AUTHORISATION:
ADMINISTRATIVE DATA

The Marketing Authorisation application is needed in view of obtaining a marketing authorisation for medicinal products for human use, submitted to:

The application form is to be used for an application for a marketing authorisation of a medicinal product submitted to:

a) The European Medicines Agency through centralised procedure, or

b) The National Agency for Medicines and Medical Devices, through national/mutual recognition/decentralised procedure.

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

Mixed applications are accepted for the centralised procedure. (Information related to the each pharmaceutical form and strength is successively provided where deemed necessary.)

Declaration and signature:

Invented name:

Pharmaceutical form:
Homeopathic stock(s) and strength(s):

Applicant:

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

It is hereby confirmed that all existing data which are relevant to the quality, safety and efficacy of the medicinal product for human use have been supplied in the dossier, as appropriate.

It is hereby confirmed that fees will be paid according to the National Agency for Medicines and Medical Devices**.

On behalf of the applicant:

.....
Signature
.....
Name*
.....
Function
.....

Site Date (year, month, day)

_____

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

*** If payment has been performed, please attach the proof in Annex 4.1- see information about payment of taxes included in the Notice to Applicants, Volume 2A, CHAPTER 7.*

1. Type of application

N O T E:

The following sections should be completed where appropriate.

1.1. This application concerns:

❍ 1.1.1. The Mutual Recognition Procedure (in accordance with Article 736 (2) of Law No. 95/2006 on healthcare reform, as amended, Title XVII „The medicinal product", as amended)

❍ YES ❍ NO

- Reference Member State:
- Date of authorisation: (yyyy-mm-dd):
- Marketing authorisation number:

(please provide a copy of the marketing authorisation – see section 5.2.)

❍ First use

- Interested Member State(s):

AT	☐	BE	☐	BG	☐	CY	☐	CZ	☐	DE	☐	DK	☐	EE	☐
EL	☐	ES	☐	FI	☐	FR	☐	HU	☐	IS	☐	IE	☐	IT	☐

LI	☐	LT	☐	LU	☐	LV	☐	MT	☐	NL	☐	NO	☐	PL	☐
PT	☐	RO	☐	SE	☐	SI	☐	SK	☐	UK	☐				

Common date of renewal:

Please specify if a waiver or amendment of PSUR-cycle (Periodic Safety Update Report) is applied for, to harmonise with a substance birthdate.

❍ „Repeat use" – first stage (Please fill in section 5.2 as well.)

▪ Interested Member State(s):

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

Please copy the boxes above for the following procedures.

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

Common date agreed for renewal:

❍ 1.1.2. <u>Decentralised procedure</u> [in accordance with Article 736 (3) of Law No. 95/2006, Title XVII „The medicinal product", as amended]

❍ YES ❍ NO

▪ Reference Member State:
▪ Reference Member State:
▪ Procedure number:
▪ Interested Member State(s):

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

▪ Please specify if a waiver or amendment of PSUR-cycle (Periodic Safety Update Report) is applied for, to harmonise with a substance birthdate.

❍ 1.1.3. <u>National procedure</u>

▪ Member State
▪ Application number, if available

▪ Please specify if a waiver or amendment of PSUR-cycle (Periodic Safety Update Report) is applied for, to harmonise with a substance birthdate.

1.2. This is an application for variation of a marketing authorisation in place with reference to the Order of the Minister of Health No. 874/2006, where applicable.

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

❍ NO (please complete Section 1.3 only)

Please state:

☐ 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, as amended.

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

- Name of the Marketing Authorisation Holder:
- Invented name, strength, pharmaceutical form of the existing medicinal product:
- Marketing Authorisation number:

1.3. This application for Marketing Authorisation is submitted in accordance with the following articles of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, as amended.

N O T E*:*

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, as amended (simplified registration procedure)

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

1.4. Administrative data/dossier requirements

Article 711 – Simplified authorisation procedure

Parts of the dossier	Submitted in the Authorisation dossier	
Module 1	❍	
Manufacturing authorisation	❍	
Mock ups of outer and immediate packaging and of package leaflet	❍	
Module 2	❍	
Module 3	❍	
Module 4	❍	
Justification of the product's homeopathic nature	❍	

Article 713 – Marketing Authorisation Procedure

Parts of the dossier	Existing requirements in the Authorisation dossier	
Module 1	❍	
Manufacturing authorisation	❍	
SPC in national language	❍	
Leaflet in national language	❍	
Mock ups of outer and immediate packaging and of package leaflet	❍	
Module 2	❍	
Module 3	❍	
Module 4	❍	
Justification of the product's homeopathic nature	❍	

2. Marketing authorisation application particulars

2.1. Name(s)

2.1.1. Invented name of the homeopathic medicinal product for human use

☐ 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 strengths[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 packaging size

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

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

For each type of packaging, please provide:

2.2.3.1.1. Packaging size(s):

N O T E:

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 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)

2.3. 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, as amended]

❍ 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 National Agency for Medicines and Medical Devices reserves the right to apply only those categories provided for in Law No. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, as amended.

_____

* For further information, please check Article 781 of Law No. 95/2006, Title XVII „The Medicinal Product", as amended.

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 for healthcare professionals only

❍ Promotion to the general public and healthcare 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
☐ 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 Agency for Medicines and Medical Devices during authorisation procedure in Romania:

Name:
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 Agency for Medicines and Medical Devices, 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 4.4).

2.4.4. Qualified person for Pharmacovigilance in the EEA

Name:
Company name:
Address:
Country:
Telephone 24 h:
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 amended **(**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 (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 the 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

(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, as amended):

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

  - Name of qualified person:
  (if not mentioned in the 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: ❍ NO ❍ YES

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 Pharmacopoeia 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 EMA/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, as amended. (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 manufacturing 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 manufacturing 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

2.6. 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*	Quantity	Unit	Reference/Monograph standard
1.			
2.			
3.			
etc.			

Name of excipients**	Quantity	Unit	Reference/Monograph standard
1.			
2.			
3.			
etc.			

*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

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

NONE ☐

Name	Function* HSA	EX	R	Animal origin susceptible to TSE**	Other animal origin	Human origin	Certificate of suitability for TSE (State no.)	
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. For national applications, please complete the section below, in accordance with Article 702 (4) m)-o) of Law No. 95/2006, Title XVII, The medicinal product, as amended.

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, as amended).

❍ 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.

* '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 No. 98/C229/03 on the Community marketing authorisation procedures for medicinal products.

☐ 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:
Grounds 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:
Grounds for withdrawal:

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

Country:
Date of suspension/revocation (yyyy-mm-dd):
Grounds 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 the 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:
Grounds 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:
Grounds for withdrawal:
☐ Countries whose competent authorities have suspended/revoked authorisation of the medicinal product
Country:
Date of suspension/revocation (yyyy-mm-dd):
Grounds for suspension/revocation:
Invented name:

4. Attached 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 748 of Law No. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, as amended (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 the written confirmation of the active substance manufacturer to inform the applicant in case of the modification of the manufacturing process or specifications, in accordance with the Annex to the Order of the Minister of Public Health No. 906/2006 on approval of the Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products, as amended (transposing the Annex to Directive 2003/63/EC of 25 June 2003, amending Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001, related to the Community Code concerning medicinal products for human use)

☐ 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 Authorisation(s) granted in an EEA country or third country under Article 702 (4) m)-o) of Law No. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, as amended, 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, mentioned in section 2.5.1, and from the qualified person of each manufacturing authorisation holder (i.e. located in EEA), mentioned 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, operating in accordance with the Rules on Good Manufacturing Practice for active substances. This does not apply to Blood or blood components.

ANNEX 3
to Regulations

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

AUTHORISATION VIA NATIONAL PROCEDURE (MRP) ☐ Authorisation number via MRP[1]: _/_/__/

AUTHORISATION VIA COMMUNITY PROCEDURE: ☐

AUTHORISATION ONLY VIA NATIONAL PROCEDURE: ☐

REFERENCE MEMBER STATE

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

INTERESTED MEMBER STATE:

AT	☐	BE	☐	BG	☐	CY	☐	CZ	☐	DE	☐	DK	☐	EE	☐
EL	☐	ES	☐	FI	☐	FR	☐	HU	☐	IS	☐	IE	☐	IT	☐
LI	☐	LT	☐	LU	☐	LV	☐	MT	☐	NL	☐	NO	☐	PL	☐
PT	☐	RO	☐	SE	☐	SI	☐	SK	☐	UK	☐	None			☐

Is the medicinal product on the market?

☐ YES ☐ NO

If YES, in what Member States is it marketed[2]?

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

Invented name: Active substance(s): Pharmaceutical classification (group + ATC code): Pharmaceutical form and strength[3]: Route of administration[3]: Target species[3]: MA Number[3]:	Name and address of the Marketing Authorisation Holder: Name and address of the contact person[4]: Telephone: Fax: E-mail: Applicant's reference:

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

1 For medicinal products for human use: number to be completed by the Marketing Authorisation Holder, reflecting the correct sequence of the number within the Mutual Recognition Procedure, in accordance with Volume 2A, Chapter 2.7. Numbering System for the Procedures for Mutual Recognition and Decentralised Procedures, in accordance with the overview on the European Commission website (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm).

2 For medicinal products authorised through centralised procedure, a separate Annex shall be submitted, containing a list of EU Member States/Norway/Iceland where the respective product is marketed.

3 For centrally authorised products, the above information, including container and packaging size(s), should be provided as a table in a separate Annex (according to Annex A attached to the CHMP opinion)

4 As mentioned in section 2.4.3 or Part 1A of the dossier. If different, attach letter of authorisation.

AUTHORISED MANUFACTURERS

Authorised manufacturers (or importers) responsible for batch release in Romania/EEA (according to Articles 748 and 760 of Law No. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, as amended)

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, in accordance with Article 823 (1), Article 825, 826 and Article 827 of Law 95/2006, as amended, 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, as amended, if different from above:

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

Further sites can be detailed 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 below, in the same format as shown above.
Manufacturer(s) of active substance(s)
NOTE: All manufacturing sites involved in the manufacturing process of each source of active substance should be listed. Importer or supplier details alone are not sufficient.

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

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

QUALITATIVE AND QUANTITATIVE COMPOSITION (ACTIVE SUBSTANCE AND EXCIPIENTS)
(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 substances separately from the excipients.

Name of the active substance(s)*	Quantity	Unit	Standard monograph

Name of the excipient(s)*	Quantity	Unit	Standard monograph

Overdose details shall not be included in these forms; these shall be stated below:
- active substance(s)
- excipient(s)

*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.

[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 SPC TEXT	PROPOSED SPC TEXT

DOCUMENTE ATAŞATE CERERII DE REÎNNOIRE

Module 1:

☐ 1.0. Cover letter

☐ 1.1. Table of contents

☐ 1.2. Renewal Application Form with the following annexes:

☐ A list of all authorised product presentations for which renewal is required in tabular format

Details related to contact persons:

☐ • Qualified person in the European Economic Area (EEA) for Pharmacovigilance;

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

☐ • Contact person for scientific service in the EEA in charge of information about the marketed medicinal products.

☐ • 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/II variations, approved or pending; extensions, notifications under Article 771 (3) of Law no. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, as amended; urgent safety restrictions, giving the procedure number (where applicable), date of submission, date of approval (if approved) and brief description of the changes

☐ • Chronological list of follow-up measures and, for centrally authorised medicinal products, any specific obligations submitted from the date of authorisation/latest renewal, stating the application field, status, date of submission and date of conclusion (if applicable)

☐ • Reviewed list of follow-up measures for post-authorisation remainders/commitments and, for centrally authorised medicinal products, any specific obligations and a signed (if applicable) letter of commitment

☐ • A statement or, when available, a certificate of GMP compliance, (authorised by the competent authority, not more than three years old, for the manufacturer(s) of the finished 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, if 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

☐ • 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) has/have been used as starting material(s) and have been obtained in accordance with the GMP Guidelines for starting materials, as adopted by the European Community[5].

☐ •Where different, a declaration by the Qualified Person of the Manufacturing Authorisation Holder(s) listed in the application form as responsible for batch release, stating that the batches have been obtained in accordance with the GMP guidelines for starting materials, as adopted by the European Community[5]

☐ 1.3.1 SPC, Labelling and Package Leaflet

☐ 1.3.2 Specimen/sample (only for centralised authorities)
☐ 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 needed – only for centrally authorised medicinal products)
☐ 1.4.3 For clinical documents(signature + CV)

Module 2:

☐ 2.3 Quality Overall Summary (Quality Expert Statement)
☐ 2.4 Non-clinical Summary (Non-clinical Expert Statement – if applicable – only for centrally authorised medicinal products)
☐ 2.5 Clinical Summary (Clinical Expert Statement)

Module 5:

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

[5]In case of several qualified persons, a single statement of one of the qualified persons, related to the fact that the active substance(s) used as starting material(s) has/have been obtained in accordance with the Guidelines on the Good Manufacturing Practice for starting materials, as adopted by the European Community, provided that:

- The statement is signed by all concerned qualified persons;
- The statement is based on a technical agreement in accordance with the description in chapter 7 of the GMP Guideline and the qualified person making the statement is the one assigned by the agreement as specifically responsible for the compliance with the GMP Guideline on compliance with GMP Guidelines on account of the active substance manufacturer(s).

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, as amended. The product conforms with 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 in accordance with NAMMD payment rules Amount/Currency:

Main signatory…… Function……..

Print name…… Date

Second signatory…….. Function……...

(where appropriate)

Print name…… Date