MINISTRY OF HEALTH

ORDER
regarding the approval of the Regulations on the granting of marketing authorizations by NMA for medicinal products for human use already authorized in the European Union Member States following the decentralized procedure

Taking into consideration the provisions of Art. 28, of the Government Emergency Ordinance No. 152/1999 on medicinal products for human use, approved with changes and completions through the Law No. 336/2002 with further changes and completions and of Art. 10, paragraph (9) of the Government Ordinance No. 125/1998 regarding the setting up, organization and functioning of the National Medicines Agency, approved with changes and completions through the Law No. 594/2002 with further changes and completions

Seeing the approval report of the Pharmaceutical General Direction, Pharmaceutical Inspection and Medical Devices No. OB. 1.770/2004,

In accordance to the Government Decision No. 743/2003 regarding the organization and functioning of the Ministry of Health with further changes,
Minister of Health emits the following Order:

Art. 1. –The Regulations on the granting of marketing authorizations by NMA for medicinal products for human use already authorized in the European Union Member States following the decentralized procedure are approved in accordance with the Annex, that is part of the present Order.

Art. 2. – At the date of entering into force of the present Order, any other contrary disposition is annulled.

Art. 3. – The present Order will be published in the Official Monitor of Romania, Part I.

Minister of Health
Ovidiu Brînzan

Bucharest, 21 February 2004
No. 181

ANNEX

REGULATIONS

on the granting of marketing authorizations by NMA for medicinal products for human use already authorized in the European Union Member States following the Decentralized Procedure

CHAPTER I
Introduction

Art. 1. - The present Regulations describe the simplified procedure for marketing authorization which can be used by the National Medicines Agency *(NMA),* as a competent authority of CADREAC (Collaboration Agreement between Drug Regulatory Authorities in European Union Associated Countries), for granting a Marketing Authorization for medicinal products for human use, already authorized in the European Union (EU) Member States, following the Decentralized Procedure, including subsequent variations and renewals, further named *CADREAC Simplified Procedure*.

Art. 2. - The use of CADREAC Simplified Procedure comes from the assumption that differences in medical practice between the EU Members States and Romania are generally not of major importance for public health, hence the assessment of the EU Reference Member State can be assumed to be relevant by the NMA.

Art. 3. - The CADREAC Simplified Procedure, described in the present Regulations, offers the possibility of harmonization the Summary of Product Characteristics (SPC), leaflet and documentation of medicinal products for human use authorized in Romania with SPC, leaflet and documentation of medicinal products for human use authorized in the EU Member States following the Decentralized Procedure, creating the premises for harmonizing the generic medicinal products that will appear in the future for an International Non-proprietary Name (INN), contained in the respective innovative medicinal product.

CHAPTER II

General Provisions

Art. 4. – The use of the CADREAC Simplified Procedure to authorize in Romania a medicinal product for human use is recommendable, but not obligatory, either for the applicant or for NMA.

Art. 5. – The CADREAC Simplified Procedure is initiated by an applicant, by virtue of submission of an application for marketing authorization to NMA, with an additional procedure specific documentation.

Art. 6. – The use of the CADREAC Simplified Procedure described in the present Regulations, does not relieve the NMA from its responsibilities as they are mentioned in the Government Emergency Ordinance No. 152/1999 on medicinal products for human use, approved with changes and completions through the Law No. 336/2002 with further changes and completions, regarding the granting of Marketing Authorizations, the approval of variations and renewals and the supervisions of safety measures within Romania territory.

Art. 7. –Medicinal products can be introduced in the CADREAC Simplified Procedure based on three options:

a) only medicinal products submitted for a Decentralized Procedure in the EU Member States with full dossier and submitted for the CADREAC Simplified Procedure to NMA also with full dossier, for their line extensions such as: different strengths, pharmaceutical forms, ways of administration and active substance modification subsequent to the Marketing Authorization of the first product of the line;

b) medicinal products mentioned under letter a) plus line extensions approved in the EU through Decentralized Procedure for the first medicinal product of the line authorized through Decentralized Procedure in EU, based on a full dossier, but the first product of the line is not harmonized in Romania with the medicinal product authorized in EU; the CADREAC Simplified Procedure applied to the line extension can therefore start only after harmonization of the first product in line, achieved through variations;

c) all products submitted for the CADREAC Procedure, including generics.

Art. 8. – The NMA option regarding medicinal products for human use, which can be subject of the CADREAC Simplified Procedure, is mentioned in ANNEX No. 3.

Art. 9. – The NMA can decide whether to start the CADREAC Simplified Procedure after the completion of the Mutual Recognition Procedure by the EU Concerned Member States, for example after the day 90, further described as the first variant, or after the issuing of the Marketing Authorization by the EU Reference Member State, further described as the second variant.

Art. 10. – The option chosen by the NMA is mentioned in the ANNEX No. 3.

Art. 11. – The basic principle of the CADREAC Simplified Procedure is based on the fact that the dossier and the SPC submitted for marketing authorization, as well as post-approval development, urgent safety measures and variations - are identical in Romania with the ones accepted by the EU Reference Member State, fact that must be guaranteed by the applicant.

Art. 12. – (1) The only differences acceptable for the medicinal products authorized in Romania through the CADREAC Simplified Procedure in comparison with the conditions in which the medicinal products were authorized in EU through the Decentralized Procedure are:

-the name of the medicinal product;

-the name of the Marketing Authorization Holder;

-the number of approved packaging sizes for the Romanian market could be smaller than the authorized number in the EU.

(2) Classification for supply of medicinal product is established by the NMA.

Art. 13. – The EU Reference Member State, should make the Updated Assessment Report available to the applicant.

Art. 14. – (1) The EU Reference Member State should provide the NMA with all necessary information, also in the post-approval phase, (rapid alert and urgent safety restrictions), via the applicant or directly, based on the declaration on information sharing of the Marketing Authorization Holder from the EU Reference Member State.

(2) With a view of communication between NMA and the competent authorities from the EU Member States where the respective medicinal product is authorized, contact persons in charge of this liaison should be nominated.

Art. 15. – In cases when questions or concerns are raised by the NMA to the EU Reference Member State assessment report, additional documents to the initial dossier may be required from the applicant, or an additional assessment according to the current national procedure may be carried out.

Art. 16. – If the second variant of the CADREAC Simplified Procedure is chosen, and the respective procedure is pending at NMA and EU Concerned Member State(s) in parallel, experts and observers of the NMA will be allowed to participate in break-out sessions of the Mutual Recognition Facilitation Group (MRFG), based on a written agreement of the applicant, in the EU Reference Member State, presented in the format described in ANNEX No. 1.

Art. 17. – The duration of the evaluation procedure with the view marketing authorization, is specified in ANNEX No. 3.

Art. 18. – All requirements for dossier submission, are provided in the Regulations on the marketing authorization, supervision, advertising, labeling and

the leaflet for medicinal products for human use, approved by the Minister of Health and Family Order No. 263/25.03.2003; requirements on fees and tariffs, which are to be paid for marketing authorization are provided by the Government Decision No. 541/1991 and of the NMA Administrative Council Decision No. 15/15 May 2001.

CHAPTER III

Responsibilities of the concerned parties

Art. 19. – The applicant or the Marketing Authorization Holder in Romania will guarantee that:

a) the dossier submitted is identical to the dossier submitted in the EU Concerned Member States;

b) the approval mentioned in ANNEX No. 1 from the manufacturer of the active substance who has the restricted part of the Drug Master File (DMF) will be available, if the European DMF procedure was used;

c) the medicinal product authorized in Romania will be kept identical with the one authorized in the EU, in the post-authorization phase;

d) all necessary information, on the course of the Decentralized Procedure for the second variant, will be submitted to NMA in time.

Art. 20. – The Marketing Authorization Holder in the EU Reference Member State will sign an approval, presented in the format described in ANNEX No. 1, regarding the information sharing and the participation of the NMA experts and observers to the MRFG break-out sessions, whenever necessary; this approval will be sent to the competent authorities from the EU Reference Member State and a copy of it will be sent to the NMA.

Art. 21. – The EU Reference Member State, will make available the Updated Assessment Report and the post-approval information (rapid alert and urgent safety restrictions), to the EU Marketing Authorization Holder, whenever necessary.

Art. 22. – NMA will keep information generated during the CADREAC Simplified Procedure confidential.

Art. 23. – (1) NMA will send a report on the outcome of the CADREAC Simplified Procedure in Romania, in the format presented in ANNEX No. 2, to the EU Reference Member State and a copy to the CADREAC Secretariat.

(2) In case of disagreement of opinion with the evaluation result in EU, or acceptance of modifications other than those defined in art. 12, paragraph (1), of the present Regulations, the report will include a justification and will be also sent to the other competent authorities from CADREAC.

CHAPTER IV
Initiation of the CADREAC Simplified Procedure

Art. 24. – (1) The Marketing Authorization Holder in the EU Reference Member State, initiates the CADREAC Simplified Procedure and notifies the competent authority in EU Reference Member State, that an application will be submitted to the NMA and declares that the competent authority in EU Reference Member State will make available to the NMA any information on the quality, safety and efficacy of the mentioned product.

(2) In the case the applicant uses the second variant of the CADREAC Simplified Procedure, he will also confirm that he agrees with the participation of the NMA experts at the break-out session of MRFG, as mentioned in ANNEX No. 1.

CHAPTER V

Submission of the authorization application for the CADREAC Simplified Procedure

Art. 25. – The variant for the CADREAC Simplified Procedure chosen by NMA is defined in the ANNEX No. 3.

Art. 26. – The submission of the documentation must comply with the NMA administrative requirements, as specified in Regulations on the marketing authorization, supervision, advertising, labeling and the leaflet for medicinal products for human use.

CHAPTER VI

The first variant for the CADREAC Simplified Procedure

Art. 27. – The authorization application for the first variant of CADREAC Simplified Procedure can be submitted anytime after the completion of the respective Decentralized Procedure in the EU, when the Updated Assessment Report is available.

Art. 28. – The applicant who intends to authorize in Romania a medicinal product authorized in EU through Decentralized Procedure using the first variant of CADREAC Simplified Procedure, has to submit to the NMA the following documents:

a) Marketing Authorization application in NMA specified format, required by the Regulations on the marketing authorization, supervision, advertising, labeling and the leaflet for medicinal products for human use, together with the administrative data and the samples requested by the NMA, according to the same Regulations;

b) the authorization documentation identical to the one submitted to the competent authorities from the EU Concerned Member States within the Decentralized Procedure;

c) the consolidated list of the questions raised by the EU Concerned Member States within the Decentralized Procedure together with the answers submitted by the applicant (day 65 responses to questions raised by Concerned Member States within the Decentralized Procedure) and later responses;

d) the Updated Assessment Report of the competent authority in EU Reference Member State, including the harmonized SPC ; if the European DMF procedure has been used, the assessment report on the restricted part of the DMF should be requested from the EU Reference Member State directly;

Art. 29. – In case there is only EU Reference Member State Assessment Report available, the applicant should provide the NMA the following information regarding the Decentralized Procedure:

a) a list with the EU Concerned Member States;

b) the Decentralized Procedure history;

c) the minutes of the break-out sessions of the MRFG, if applicable;

d) information about the reasons of withdrawal, if applicable ;

e) the letter of the EU Reference Member State about the completion of the procedure with SPC attached.

Art. 30. – In case variations have been approved after conclusion of the Decentralized Procedure, a list of all these variations should be submitted to the NMA attached to the marketing authorization application; the documentation submitted in the EU Member States, to support these variations, the assessment report/reports of the variation(s), if applicable, and an acceptance letter of the variation(s) by the competent authorities in the EU Member States should be attached to the original dossier.

Art. 31. – In case the marketing authorization application is submitted to NMA later then 9 months after the authorization in the EU Reference Member State and concerns a new active substance, the latest available periodic safety updated report should be submitted to NMA as well.

Art. 32. –A list of post-authorization commitments imposed in the Decentralized Procedure, if any, and the status of their fulfillment must be submitted to NMA.

Art. 33. –The applicant should submit to the NMA a declaration referring to:

a) the commitment to collaborate with the NMA similarly as the Marketing Authorization Holder does with the competent authorities in the EU Member States and to keep the medicinal product authorized by the NMA identical with the medicinal product authorized by the competent authorities in the EU Member States, respectively to notify and implement all urgent safety measures simultaneously in the EU Member States and in Romania, and to submit and implement all variations, once accepted in the EU Member States, without unnecessary delay, in the post-authorization period;

b) the fact that the file submitted to NMA is identical to the one submitted in the EU Concerned Member States in the Decentralized Procedure, including all information submitted to support any variation which has been applied for and accepted at the time of submission of the application in Romania, as well as the information concerning post-authorization commitments, if any, respectively if the documentation reflects the situation of the product in the EU Member States, at the time of submission of the application to the NMA;

c) the fact that the SPC proposed in Romanian is the translation of the last SPC approved in Decentralized Procedure.

Art. 34. – The applicant will submit the declaration of the Marketing Authorization Holder in the EU Reference Member State and, if necessary, the approval from the Holder of the restricted part of the DMF, presented in the format described in ANNEX No. 1.

Art. 35. – The evaluation procedure used by the NMA in case of the marketing authorization applications for the first variant of the CADREAC Simplified Procedure is the procedure described in the Regulations on the marketing authorization, supervision, advertising, labeling and the leaflet for medicinal products for human use.

Art. 36. – The NMA will send the report on the outcome of the CADREAC Simplified Procedure in Romania in the format presented in ANNEX No. 2, to the competent authority from the EU Reference Member State and a copy of the report to the CADREAC Secretariat.

CHAPTER VII

The second variant of the CADREAC Simplified Procedure

Art. 37. – The applicant is advised to consult ANM before the submission of the application for the second variant.

Art. 38. – The application for the second variant may be submitted after the issuance of the assessment report by the competent authority in the EU Reference Member State.

Art. 39. – The applicant that has the intention to authorize in Romania using the second variant of the CADREAC Simplified Procedure, a medicinal product that is in Mutual Recognition Procedure in EU and has a Marketing Authorization only from the EU Reference Member State, should submit the following documents to the NMA:

a) marketing authorization application in specific NMA format, as provided in the Regulations on the marketing authorization, supervision, advertising, labeling and the leaflet for medicinal products for human use, together with the administrative data and the samples requested by the NMA in accordance with the same Regulations;

b) authorization documentation identical with that submitted to the competent authorities in the EU Concerned Member States in the Decentralized Procedure ;

c) the assessment report of the competent authority in the EU Reference Member State, including the SPC approved by the competent authority in the EU Reference Member State, in English; if the European DMF procedure has been used, the assessment report on the restricted part of DMF should be requested from the EU Reference Member State directly.

Art. 40. – The applicant should submit to the NMA a declaration referring to:

a) the commitment to collaborate with the NMA similarly as the Marketing Authorization Holder does with the competent authorities in the EU Member States and to keep the medicinal product authorized by the NMA identical with the medicinal product authorized by the competent authorities in the EU Member States, respectively to notify and implement all urgent safety measures simultaneously in the EU Member States and in Romania, and to submit and implement all variations, once accepted in the EU Member States, without unnecessary delay, in the post-authorization period;

b) the fact that the file submitted to NMA is identical to the one submitted in the EU Reference Member State and in the EU Concerned Member States in the Decentralized Procedure, if applicable;

c) the fact that he will inform the NMA on each step of the Decentralized Procedure.

Art. 41. – The applicant will submit the declaration of the Marketing Authorization Holder in the EU Reference Member State and, if necessary, also, the

approval of the Holder of the restricted part of DMF, presented in the format described in ANNEXA No. 1.

Art. 42. – The applicant will submit to NMA all information regarding the Decentralized Procedure, in due time, in accordance with the procedure and the deadlines described in the revised version of the Guideline for Good Practice in Mutual Recognition Procedure.

Art. 43. – The evaluation procedure used by the NMA in case of the marketing authorization applications for the second variant of the CADREAC Simplified Procedure is the procedure described in the Regulations on the marketing authorization, supervision, advertising, labeling and the leaflet for medicinal products for human use.

Art. 44. – The NMA will send the report on the outcome of the CADREAC Simplified Procedure in Romania in the format presented in ANNEX No. 2, to the competent authority from the EU Reference Member State and a copy of the report to the CADREAC Secretariat.

CHAPTER VIII

Variations to the Marketing Authorization of the medicinal products which have been authorized through the CADREAC Simplified Procedure

Art. 45. – In accordance to art. 19 paragraphs c) the Marketing Authorization Holder will submit and implement the variations in Romania, the same way as in the EU Member States.

Art.46. – The documents submitted to the NMA by the Marketing Authorization Holder for the notification or approval of the variations are:

a) the notification or application for approval of the variations, in the NMA specific format, provided in the Regulations on the evaluation procedure of the variations to the terms of the Marketing Authorization for medicinal products for human use, approved by the Minister of Health Order No. 89/02.02.2004, together with the administrative data and samples requested by the NMA ;

b) the acceptance letter of the respective variation, sent by the EU Reference Member State to the Marketing Authorization Holder and, if necessary, to the EU Concerned Member State;

c) updated Assessment Report of the EU Reference Member State or amendments to the assessment report or the assessment report of the variation, if issued;

d) the application supporting documentation identical with that is or has been submitted within the Decentralized Procedure for the respective variation;

e) updated SPC in English, in the case that the variation determined its modification, and the SPC, the leaflet and/or the labeling text, if necessary, in Romanian, with all proposed changes in comparison with the approved version highlighted.

CHAPTER IX

Renewal of the Marketing Authorizations for medicinal products authorized in Romania by CADREAC Simplified Procedure

Art. 47. – The renewal of the Marketing Authorizations of the medicinal products authorized in Romania by CADREAC Simplified Procedure is carried out in accordance with the renewal provisions of the Regulations on the marketing authorization, supervision, advertising, labeling and the leaflet for medicinal products for human use.

CHAPTER X

Retrospective inclusion in the Common CADREAC Procedure of the medicinal products approved in EU through Decentralized Procedure

Art. 48. – Any medicinal product authorized in Romania through national procedure, but also authorized in the EU by the Decentralized Procedure, can be harmonized, retrospectively, in Romania with its status in the EU through variation(s) to the Marketing Authorization sent by the Marketing Authorization Holder and implemented in Romania.

Art. 49. – The principles of the procedure and responsibilities of the interested parties are applied in the same way as in the case of the initiation of the CADREAC Simplified Procedure for granting the Marketing Authorization by the NMA for medicinal products for human use, already authorized in the EU Member States through Decentralized Procedure.

Art. 50. – The Marketing Authorization Holder in Romania should consult the NMA for each particular case in which the respective Retrospective Inclusion is considered.

Art. 51. – After the consultation with the NMA, mentioned in art. 50, the Marketing Authorization Holder in the EU Reference Member State, informs the competent authority in the EU Reference Member State, that the respective medicinal product will be harmonized in Romania in accordance with its status in the EU Reference Member State, and declares that the competent authority in the EU Reference Member State can make available for the NMA any information concerning the quality, safety and efficacy of the respective medicinal product and

agrees with the participation of the NMA experts and observers to the break-out session of the MRFG, if necessary.

Art. 52. – The documents that should be submitted to the NMA by the Marketing Authorization Holder for the Retrospective Inclusion are the following:

a) the authorization application, in the NMA specific format, as provided in the Regulations on the marketing authorization, supervision, advertising, labeling and the leaflet for medicinal products for human use, together with the administrative data and the samples requested by the NMA in accordance with the same Regulations;

b) the documents mentioned in the list for the first variant of the CADREAC Simplified Procedure.

Art. 53. – The evaluation procedure used by the NMA in the case of Retrospective Inclusion in the Common CADREAC System is the procedure described in the Regulations on the marketing authorization, supervision, advertising, labeling and the leaflet for medicinal products for human use.

Art. 54. – The NMA will send the report on the outcome of the CADREAC Simplified Procedure in Romania in the format presented in ANNEX No. 2, to the competent authority from the EU Reference Member State and a copy of the report to the CADREAC Secretariat.

Art. 55. – ANNEX No. 1-3 are part of the present Regulations.

ANNEX No.1
to the Regulations

APPROVAL

of information sharing between the competent authority of the EU Reference Member State and the NMA

Name of the product:

The Decentralized Procedure No. (Mutual Recognition Procedure):

The Marketing Authorization Holder in the EU Reference Member State *hereby notifies to* the competent authority of the EU Reference Member State, *of the submission of an application for the marketing authorization of the following medicinal product to the NMA:*

- name of the medicinal product, pharmaceutical form, strength package size(s),(differences in brand name, if any),

- proposed Marketing Authorization Holder for Romania

The Marketing Authorization Holder in the EU Reference Member State *agrees that the* competent authority of the EU Reference Member State *will make available to the NMA any information concerning the quality, safety and efficacy of the above mentioned medicinal product. The extending of this information shall not be exceeding that which is made available to the EU Member States. In case that the second variant of the CADREAC Simplified Procedure is used,* the Marketing Authorization Holder in the EU Reference Member State *agrees with the participation of the NMA experts and observers in the break-out sessions of MRFG.*

The information will be used by the NMA in accordance with the Regulations on the marketing authorization, supervision, advertising, labeling and the leaflet for medicinal products for human use, approved by the Minister of Health Order No. 263/2003.

This approval is issued at the date mentioned bellow, and remains valid for the period during which the medicinal product is authorized in the EU Member States, and in Romania respectively.

Date

Signature of the Marketing Authorization Holder

First name, family name :

Address :

NOTE:
The text in Italics should be replaced by specific data for each product.

ANNEX No. 2
to the Regulations

REPORT
on the Marketing Authorization granted by the NMA for the medicinal product subjected to the Decentralized Procedure in the EU NMA

To : the competent authority of the EU Reference Member State

Name of the product in the EU Reference Member State, the pharmaceutical form(s), strength(s) relevant to this report,
INN or common name of the active substance(s)
Number(s) of the Decentralized Procedure for the respective medicinal product
Name of the Marketing Authorization Holder from the EU Reference Member State

- ☐ Report on the acceptance of the Marketing Authorization within the Decentralized Procedure
- ☐ Report on the disagreement with the Marketing Authorization within the Decentralized Procedure *)
- ☐ Report on refusal of the variation*)
- ☐ Report on the Retrospective Inclusion of the medicinal product in the data base of the medicinal product approved, according to the CADREAC Simplified Procedure
- ☐ Request addressed to the EU Reference Member State.

Name of the product in ROMANIA
Number(s) of the Marketing Authorization(s) in Romania
Date of issuance of the marketing authorization decision in Romania
Name of the Marketing Authorization Holder in Romania
Pharmaceutical form(s)/, strength(s), package size(s) authorized in Romania

Modifications of SPC and of leaflet (specifying differences, except differences on the name of the product, the Marketing Authorization Holder, national Marketing Authorization number)

Modifications of labeling (specifying differences, except differences on the name of the product, the Marketing Authorization Holder, national Marketing Authorization number)

Explanatory Note *):

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Annexes

Data: The signature of the NMA responsible person

NOTE:

The text in Italics should be replaced by specific data for each product

ANNEX No. 3
to the Regulations

Specific NMA requirements

Country	Scope of the CADREAC Simplified Procedure	Timing of the submission	Expected handling net time for finalizing the CADREAC Simplified Procedure	Language of the dossier	Number of copies to be submitted	The possibility to send documentation electronically	Need of samples and/or substance
Romania	**Only for medicinal products submitted for Decentralized Procedure IN EU Member States and submitted for CADREAC Simplified Procedure to the NMA also with full dossier, and for their extensions[art7, lit. a) of the present Regulations] and for the generics authorized in the EU through Decentralized Procedure**	**Variant I**	**6 months**	**English, Romanian**	**1 copy for all the documentation 2 copies for the Updated Assessment report of the EU Reference Member State, final SPC of the final Decentralized Procedure, proposed SPC, leaflet and labeling in Romanian**	**Possible submission of the dossier in Pharmbridge-DAMOS, CD-ROM format, together with the documentation on paper, of identical content; SPC and leaflet (final approved version) in Romanian, on a 3,5 inch diskette using Word for Windows**	**- 2 samples of the medicinal product presented in outer packaging; -reference substance (if referred to in the testing procedure)**