DECISION

No. 10/29.02.2008

on approval of the Guideline on the marketing authorisation of medicinal products for human use on the basis of co-operations, starting from an existing marketing authorisation

The Scientific Council of the National Medicines Agency,
set up based on Order of the Minister of Health No. 485/09.05.2005, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 29.02.2008 in accordance with Article 10 of Government Ordinance No. 125/1998 related to the set-up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002, with further changes and completions, agrees on the following

DECISION

Art. 1. – The Guideline on the marketing authorisation of medicinal products for human use on the basis of co-operations, starting from an existing marketing authorisation is approved, according to the annexes which are integral part of this decision.

Art. 2. – On the date of the coming into force of this Decision, Scientific council Decision No. 22/27.09.2002 on approval of Regulations on the marketing authorisation of medicinal products for human use based on a cooperation, starting from an existing marketing authorisation is repealed.

Art. 3. – This Guideline applies to the marketing authorisations in case of cooperation, submitted to the National Medicines Agency after the date of the coming into force of this decision.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE
on the marketing authorisation of medicinal products for human use on the basis of co-operations, starting from an existing marketing authorisation

CHAPTER I
Introduction

Art. 1. - (1) This Guideline establishes the marketing authorisation procedure for medicinal products for human use in case of co-operations, starting from an existing Marketing Authorisation (MA).

(2) This Guideline only applies to medicinal products for human use authorised through national procedure.

Art. 2. – Co-operations may take place between the existing Marketing Authorisation Holders (MAHs) and another MAH or between an existing MAH and a manufacturer.

Art. 3. – Any type of cooperation which leads to the proposal of a new marketing authorisation should be mentioned in the marketing authorisation, in accurate terms.

Art. 4. – This Guideline also includes the situations in which a MAH requires multiple marketing authorisations, starting from an existing marketing authorisation.

Art. 5. – Any type of requirement referring to the marketing authorisation of a medicinal product starting from an existing MA, shall be subject to an evaluation in accordance with the provisions of this Guideline.

Art. 6. - (1) Based on the favourable decision concerning the marketing authorisation of the medicinal product for which a certain type of cooperation has been mentioned, the National Medicines Agency (NMA) issues a new MA, describing the cooperation's terms, the way they were exposed in the marketing authorisation application for the concerned medicinal product.

(2) The new MA refers to a new MAH in case of a co-operation between two different MAHs (there are no changes concerning the manufacturing of the finished product), as well as in the case of co-operation between a MAH and a manufacturer (changes take place in the manufacture of the finished product), the manufacturing becoming a MAH.

(3) The new MA refers to the same MAH as the one mentioned in the existing MA, in case of multiple Marketing Authorisations.

CHAPTER II

Procedure for marketing authorisation of medicinal products for human use on the basis of co-operations, starting from an existing marketing authorisation

Art. 7. – In view of implementing a procedure for marketing authorisation of medicinal products for human use on the basis of co-operations, starting from an existing MA, should be submitted to the NMA – Records, Distribution Bureau (RDB) within the Evaluation-Authorisation Department (EAD), the authorisation application, in the format exposed in Annex 1 of Minister of Public Health Order No. 895/2006 on the approval of the Regulations concerning the marketing authorisation and the supervision of medicinal products for human use, adequately filled in under all relevant sections, accompanied by the tariff form and by the support documentation issued in accordance with provisions of Annex 1 of the present Guideline.

Art. 8. - (1) RDB checks under administrative aspect the authorisation application and the specific documents included in the application.

(2) If the marketing authorisation application and the attached documents do not meet the legislative requirements in force, as well as the provisions of this Guideline, the application is dismissed, and the reason for dismissal shall be mentioned in the receipt book.

Art. 9. – After having paid the tax and the authorisation fee, having received the confirmation of the NMA Economic Department (ED) concerning the encashment of the tax and the authorisation fee, the marketing authorisation application accompanied by the support documentation is assigned to the Quality Assessment Service – national procedures and co-operations (QAS-NPC) within the EAD.

Art. 10. - (1) The QAS-NPC assesses whether the support documentation respects the conditions implied in this Guideline and examines whether all conditions in view of release of a new MA are met.

(2) If all requirements in view of the release of a new MA are met, it will be released in maximum 210 days as of the payment confirmation by the ED.

Art. 11. - (1) In case the support data of the marketing authorisation application are incomplete, the NMA issues requirements in view of completing the support documentation.

(2) The timeframe mentioned under Art. 10 is suspended until the transmission of the completions required by the assessor.

Art. 12. – The evaluation process of the marketing authorisation dossier for the concerned medicinal product ends by issuing a final report containing the recommendation for authorisation or withdrawal of the authorisation.

Art. 13. - (1) In case of necessity of an inspection to be carried out at the manufacturing site(s) by the inspectors of the NMA Pharmaceutical Inspection Department (PID) or the verification of the control methods, during the marketing authorisation procedure of a medicinal product in case of a co-operation, the provisions of the Minister of Public Health Order No. 895/2006 on the approval of regulations concerning the marketing authorisation and the surveillance of medicinal products for human use shall be applied.

(2) The conduct of the inspection and/or the laboratory control may be requested by the assessor in those cases when the cooperation is different from the existing MA, as far as the manufacturing of the finished product is concerned.

(3) In certain cases, where needed, the NMA may require the manufacturing and control contract issued in accordance with Chapter 7 – The manufacturing and control contract from the Guideline on the Good Manufacturing Practice for medicinal products for human use, approved through SCD No. 38/2006.

Art. 14. – The final evaluation report, together with the results of laboratory testings, if required, are exposed in the Marketing Authorisation Commission meeting, which shall debate on the MA release.

Art. 15. – Following the voicing of the favourable opinion by the MAA, the issue of the MA and of the attached annexes, in accordance with provisions of Minister of Public Health Order No. 895/2006 on the approval of Regulations regarding marketing authorisation and supervision of medicinal products for human use, including complete information on the terms of cooperation, where needed.

ANNEX 1

Documents needed in view of support of the marketing authorisation application for medicinal products for human use in case of co-operations, starting from an existing marketing authorisation application, depending on the cooperation type

1. The documents needed for the support of the marketing authorisation application of medicinal products for human use in case of cooperation involving the issue of a new MA for a new MAH, deprived of modifications as far as the manufacturing process is concerned:

a) An accurate description of the cooperation’s terms

b) A copy of the existing MA (including the copy of the MA attachments and the copy of the rectification documents, where needed)

c) A cooperation agreement between parties, providing detailed information on the cooperation terms (the document should be dated and signed by both parties)

d) A declaration signed by the holder of an existing MA, related to the submission to the NMA of the marketing authorisation dossier, in view of authorisation of the respective medicinal product for the new MAH; the declaration shall also refer to submitting the support documentation of variations to MA terms to the NMA.

e) A declaration signed by the holder of an existing MA, referring to his obligation to inform the new MAH about any modification occurred in the authorisation dossier, also referring to the submission of the relevant variation application changes operated in the existing MA.

f) Proof of establishment of the new MAH within the European Union (EU)

g) documents attesting the ability of the new MAH to fulfil the responsibilities required from a MAH:

- a document for the identification of the person qualified as responsible for the pharmacovigilance activity, accompanied by the address, telephone, fax, e-mail and Curriculum Vitae of the qualified person; the qualified person responsible for the pharmacovigilance activity should permanently be at the disposal of the new MAH and should be established in Romania or the EU
- a document describing the pharmacovigilance system of the new MAH
- a document describing the scientific service responsible for the information concerning the authorised medicinal products, including address, telephone, fax
- identification document of the person/company authorised for communication between the new MAH and the NMA
- identification document of the contact person responsible for subsequent complaints concerning the product, including name, address, telephone, fax and e-mail

h)SPC, prospect, relevant labels for the new MAH

i) Declaration of the qualified person of the MAH, including the declaration of the qualified person of each manufacturing authorisation holder, referring to the GMP compliance of the active substance(s).

2. Necessary documents in view of supporting the marketing authorisation application for medicinal products for human use in case of co-operations implying the issue of a new MA for the same MAH (a new name for the medicinal product, involving no changes in the manufacturing of the medicinal product):

a) An accurate description of the cooperation’s terms

b) A copy of the existing MA (including the copy of the MA attachments and the copy of the rectification documents, where needed)

c) A declaration signed by the holder of an existing MA attesting that the single modification occurred when issuing the new MA refers to the medicinal product's name

d) SPC, prospect, relevant labels for the new name of the medicinal product

3. The documents needed for the support of the marketing authorisation application for medicinal products for human use in case of co-operations involving the issue of a new MA, for a new MAH in case of change of the secondary packaging site of the finished product and/or of the batches testing site and/or of the batch release site.

a) An accurate description of the cooperation terms

b) A copy of the existing MA (including the copy of the MA attachments and the copy of the rectification documents, where needed)

c) A cooperation agreement between parties, providing detailed information on the cooperation terms (the document should be dated and signed by both parties)

d) A declaration signed by the holder of an existing MA, making available the marketing authorisation dossier to the NMA, in view of authorisation of the respective medicinal product for the new MAH; the declaration shall also refer to making available the support documentation of variations to MA terms to the NMA

e) A declaration signed by the holder of an existing MA, referring to his obligation to inform the new MAH about any modification occurred in the authorisation dossier, also concerning the submission of variation applications relevant for the changes operated in the existing MA.

f) documents attesting the ability of the new MAH to fulfil the responsibilities required from a MAH:

- identification document of the qualified person responsible for the pharmacovigilance activity, including address, telephone number, fax, e-mail and Curriculum Vitae of the qualified person; the qualified person responsible for pharmacovigilance activity should permanently be at the disposition of the new holder and should be established in Romania or the EU
- document describing the pharmacovigilance system of the new MAH
- document describing the scientific service responsible for the information on the authorised medicinal products, including address, telephone, fax
- identification document of the person/company authorised for communication between the new MAH and the NMA.

- Identification document of the contact person responsible for the subsequent complaints concerning the medicinal product, including name, address, telephone, fax and e-mail

g) SPC, prospect, relevant labels for the new MAH

h) Declaration of the MAH qualified person, including the declaration of each MAH qualified person, concerning the GMP conformity of the active substance(s)

i) Proof that the site proposed for secondary packaging and/or batch testing and/or batch release is appropriately authorised for the pharmaceutical form or for the concerned medicinal product, such as:

- for a packaging site within the European Economic Area (EEA): copy of the valid manufacturing authorisation
- for a packaging site outside the EEA where there is a mutual recognition agreement between that country and the EU: copy of the valid manufacturing authorisation, of the GMP certificate or of the equivalent document issued by the relevant competent authority
- for the packaging site outside the EEA where there's isn't a mutual recognition agreement: a GMP declaration or equivalent, released by a competent authority of a EEA member state or the copy of a favourable inspection report issued by a competent authority in a PIC/S country
- for the site where the batch testing and/or batch release is carried out, within the EEA: copy of the valid manufacturing authorisation or an official accreditation as a testing laboratory or an equivalent document
- for the site where batch testing is carried out, outside the EEA where there is a mutual recognition agreement between that country and the EU: copy after a valid manufacturing authorisation, after the GMP certificate or after the official document attesting the accreditation as a testing laboratory or after the equivalent document issued by the relevant competent authority

j) original declaration attesting that the transfer of the control methods from the previous site to the new one or to a novel testing site has been finalised accordingly (where needed, the NMA may carry out an inspection for the verification of the compliance with the control methods transfer)

k) the document concerning the date of the most recent satisfactory inspection referring to the packaging site, carried out by a competent authority in an EU member state or in another country having a mutual recognition agreement in the EU.

4. Documents needed for the support of the marketing authorisation application for medicinal products of human use in case of a cooperation involving the issue of a new MA for a new MAH in case of change of the primary packaging site, with or without consecutive changes concerning the

secondary packaging, batch testing and release The requirements specified under point 3) are applicable, as well as the following:

a) document on the date and purpose of the last satisfactory inspection concerning the packaging site (please specify whether this is about a medicinal product, or a certain pharmaceutical form etc.), carried out by a competent authority in a member state or in a country where a GMP mutual recognition agreement between that country and the EU during the three previous years is established.

b) validation report of the manufacturing process in the new conditions

c) declaration signed by the new MAH attesting that no changes in the quality/source of primary package materials have occurred.

In case of modifications brought to the provider of primary package materials, the relevant sections of parts IIA, IIC, IIF or the equivalent in CTD format shall be transmitted.

5. Necessary documents in view of support of the marketing authorisation application for medicinal products for human use in case of co-operations involving the issuing of a new MA for a new MAH, in case of the modification of the manufacturing site relating to certain stages of the manufacturing process or for the entire manufacturing process of the finished product with or without consecutive modifications concerning the primary and secondary packaging, batch testing and release.

The requirements specified under (4) are applicable, as well as:

a) Declaration signed by a holder of an existing MA and by the new MAH attesting that the specifications of the finished product haven't changed (when released and for the availability period); a copy after the specification for release and for the availability period shall be attached.

b) data concerning the batch analysis for a manufacturing batch and two pilot-scale batches or two manufacturing batches (at the new manufacturing site) and comparative data relating to the three previous batches obtained at the previous manufacturing site; data relating to the following two manufacturing batches should be available upon request

c) declaration signed by the holder of an existing MA and by the new MAH attesting that no changes have occurred during the manufacture of the finished product, at the new manufacturing site

d) if changes have been made in the manufacture of the finished product, at the new manufacturing site proposed (provided that the manufacturing principle stays the same) the following data shall be transmitted:

- The modified section of part IIB or the equivalent in CTD format

- For solid dosage forms: data on the dissolution profile for a representative production batch and comparative data on the last three manufacturing batches obtained at the previous site; the data for the two following manufacturing batches should be available upon request.

Disaggregated data are accepted for herbal medicinal products.

- Justification for lack of submission of a new bioequivalence study, according to the Guideline on the investigation of the bioavailability and bioequivalence.
- Data of batch analysis (in comparative tabulated format) for at least one batch manufactured through the current manufacturing process approved as well as through the modified process; data on the two following production batches should be available upon request
- Stability data for the finished product manufactured through the modified manufacturing process (modified section of part IIF or the equivalent in CTD format)

e) declaration signed by the holder of an existing MA and by the new MAH occurring that no changes have been made in the composition of the finished product, quality and/or source of starting materials (active substance(s) and auxiliary substance(s)).

In case of the cooperation mentioned under point 5, modifications in the composition of the finished product and in the quality of the starting materials are not accepted.

In case modifications of the providers of starting materials at the new proposed manufacturing site occur, the following data shall be transmitted:

a) modified page(s) of part IIC or equivalent CTD format

b) a declaration signed by the new MAH according to which, route of synthesis (or in case of the phytotherapeutic medicinal product, where needed, the manufacturing method, geographic source, the process of obtaining the herbal product and the manufacturing method), quality control procedures and specifications of the active substance and starting material/reagent/intermediate product used in the manufacturing process of the active substance (if applicable) coincide with the already approved ones

c) analysis data of the active substance batches (in comparative table format) for at least 2 series (minimum at pilot-scale) from the currently approved manufacturing site and from the proposed manufacturing site

d) a TSE certificate of compliance with the European Pharmacopoeia (Ph. Eur.) for each new source of starting materials or, if applicable, documents attesting that the respective starting material with TSE risk has been assessed by a competent authority and is compliant with the Guideline in force on the risk minimisation of transmission of animal spongiform encephalopathy agents via medicinal products for human use

e) a certificate of conformity of the Ph. Eur. (new or revised) for the active substance, if needed.

The applicants should take into account that the change of the source of active substance should not lead to the change of the finished product's specifications (at release and for the availability period).

The manner of presentation of the support documentation in case cooperation requires modification of the finished product manufacturing site, with changes in the method of preparation and/or source of starting materials and primary packaging materials, should follow the Minister of Public Health Order No. 906/2006 for approval of the analytical pharmacotoxicological and clinical protocols concerning the testing of medicinal products.