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POSSIBILITY TO FOLLOW THE DCP FOR A 'DUPLICATE APPLICATION' OF A MEDICINAL PRODUCT IN THE MRP

**Question 1**

*If a duplicate application of a medicinal product authorised via the Mutual Recognition Procedure is submitted via the Decentralised Procedure, will the MS(s) where the application has been submitted be able to accept it?*

**Answer:** The CMDh has agreed that a duplicate application of a medicinal product authorised via the Mutual Recognition Procedure can be accepted via the Decentralised Procedure, provided that the same Reference Member State is used.

POSSIBILITY TO FOLLOW THE DCP FOR AN EXTENSION APPLICATION OF A MEDICINAL PRODUCT IN THE MRP

**Question 2**

*Is it possible to use the Decentralised Procedure for an extension application of a medicinal product authorised via the Mutual Recognition Procedure?*

**Answer:** Yes. The CMDh has agreed that an extension application in accordance with Annex I of Commission Regulation (EC) No. 1234/2008 of a medicinal product authorised via the Mutual Recognition Procedure can be accepted via the Decentralised Procedure.

**Question 2.a**

*According to Art. 19 of Regulation 1234/2008/EC as amended it is possible to include an extension application into an existing marketing authorisation. What are the prerequisites for such an application?*

**Answer:** Usually an extension application is handled as a new marketing authorisation application under a new speciality number in the MRP procedure number and will receive a separate new marketing authorisation, e.g. as a new strength or a new pharmaceutical form, etc. In exceptional cases where no new marketing authorisation is needed the result of the line extension procedure may be included in the existing marketing authorisation which is then accordingly amended. However, this procedure is only possible in cases where all member states concerned are in agreement that this extension application can be included in the existing marketing authorisation. Otherwise these procedures will lead to a disharmonised processing of the applications resulting in different procedure numbers, different eCTD sequences etc. It is therefore strongly recommended that applicants intending to submit such an application contact the RMS and all CMS of the procedure in advance of the submission and ask for their acceptance that the extension application will be included in the existing marketing authorisation. If not all member states can agree to this approach due to national legal background it is highly recommended to submit the extension application as a new speciality to the procedure number and to later on withdraw the former marketing authorisation.
ARTICLE 17(2) OF DIRECTIVE 2001/83/EC

Question 3

Will it be possible for applicants to submit simultaneous applications for marketing authorisation through national procedures in several Member States for the same medicinal product for which an earlier marketing authorisation has not yet been granted in another Member State?

Answer: According to Article 17(2) of Directive 2001/83/EC, where a Member State notes that another marketing authorisation application for the same medicinal product is being examined in another Member State, the Member State concerned shall decline to assess the application and shall advise the applicant that Articles 27 to 39 of Directive 2001/83/EC apply.

As stated in the Notice to Applicants (Chapter 2 of Volume 2A), the Member State which has already started the examination will normally be the future Reference Member State. It is within the responsibility of the Reference Member State either to continue or to restart the procedure after receiving the information that in other MS an application for the same medicinal product by the same applicant is pending.

ARTICLE 18 OF DIRECTIVE 2001/83/EC

Question 4 (Last update: January 2016)

If an application for a marketing authorisation is submitted nationally or via the Decentralised Procedure in a MS and that MS is informed that the same medicinal product has received a marketing authorisation in another MS, will the MS where the application has been submitted be able to accept it?

Answer: According to Article 18 of Directive 2001/83/EC, where a MS is informed that another MS has authorised a medicinal product which is the subject of a marketing authorisation application, the MS concerned will reject the application unless it was submitted under the Mutual Recognition Procedure or the Decentralised Procedure (with RMS from Member State with the national marketing authorisation) and will inform the MS where the product has been authorised.

As stated under 3.2, chapter 2 of volume 2A of Notice to Applicants, differences between the SmPC, package leaflet and labelling approved in one Member State and the SmPC, package leaflet and labelling submitted in another Member State do not automatically prevent the latter from a Mutual Recognition Procedure. If these differences have no therapeutic implications (no difference in the efficacy and safety profile), i.e. both products have the same qualitative and quantitative composition in active substances (i.e. the same strength) and the same pharmaceutical form, they have to be considered as being the same and the MRP or the DCP (with RMS from Member State with the national marketing authorisation) has to be followed.

Independent national procedures can be used for extensions of authorised medicinal products as far as no a priori harmonisation has been achieved for the initial marketing authorisation.

Different dossiers for a product with the same qualitative and quantitative composition in active substances, the same pharmaceutical form and same MAH

• Different dossiers for the same medicinal product from the same MAH are not recommended and considered not to be in accordance with the principles of the single market. However, if these dossiers exist for historical reasons or due to a
merger, it is not possible to coexist in the same marketing authorisation procedure, because Article 28(1) of Directive 2001/83/EC states in this regard that "with a view to the granting of a marketing authorisation in more than one Member State, an applicant shall submit an application based on an identical dossier in these Member States".

CMDh recommends the following for handling these applications:

- Applicants should comply with Article 8(3)(1) and provide copies of any authorisation obtained for that medicinal product with the application for marketing authorisation. This should allow the Competent Authorities to verify that the provisions of Directive 2001/83/EC, are being complied with;
- The acceptance of an application for marketing authorisation for a different dossier should not lead to applications for the same product being submitted in different Member States and handled outside the principles of Mutual Recognition laid down in Chapter IV of Directive 2001/83/EC;
- The same Reference Member State should be used, where possible, also in the situation where the dossiers differ, in accordance with the CMDh recommendations on multiple/duplicate applications in MRP and DCP; if the same Reference Member State cannot be used, the CMDh recommends the use of one of the Concerned Member States involved in the previous procedure as the Reference Member State;
- Applicants can decide whether to use the Mutual Recognition Procedure or the Decentralised Procedure for the "duplicate" marketing authorisation.

Same medicinal 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"

**INFORMATION ON FEES PAYABLE TO MEMBER STATES IN THE MRP/DCP**

**Question 5**

*Which is the best way to get information on the fees payable to every MS when they act as RMS or CMS in the Mutual Recognition or Decentralised Procedure?*

**Answer:** This information is provided by national competent authorities. Addresses for receipt of fees and details of how payments are to be made are set out on the Contact Points page of CMDh website (http://www.hma.eu/69.html)

**COMMUNICATION**

**Question 6**

*How should the communication in a MRP/DCP be directed?*

**Answer:** Applicants are reminded that the Reference Member State (RMS) is the main contact point during a MRP/DCP. In case of any direct communication between Concerned Member States and local affiliates of the Applicant, the RMS should be kept informed.
GENERAL INFORMATION ON NATIONAL REQUIREMENTS

Question 7

Where can I find general information regarding national requirements for MRP/DCP?

Answer: Further to the work carried out by the Working Group on Validation Issues/National Requirements in the framework of the Mutual Recognition and Decentralised Procedures, the CMDh has published on the website the Additional data requested for new applications in MRP/DCP (http://www.hma.eu/91.html).

For information on the presentation and content of the dossier or on regulatory Guidelines, please consult Volume 2B or 2C of the Notice to Applicants, respectively. The Notice to Applicants is published in the European Commission website: http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm.

BIBLIOGRAPHICAL APPLICATIONS AND MUTUAL RECOGNITION/NATIONAL PROCEDURE

Question 8

The Decentralised or Mutual Recognition Procedures are compulsory when the same Applicant intends to market a medicinal product in more than one Member State. Can you clarify when two or more Companies are considered to be the same Applicant?

Answer: According to the Commission communication on the Community marketing authorisation procedures for medicinal products 98/C 229/03, two or more companies are considered to be the same applicant when they belong to the same mother company or group of companies or when, without belonging to the same mother company or group of companies, have concluded agreements (e.g. ‘licensees’) or exercise concerted practices concerning the placing on the market of the relevant medicinal product in different Member States.

Question 9

When a Company has sold a dossier for a medicinal product to an unrelated Company, is it possible for both Companies to apply nationally for Marketing Authorisation in different Member States?

Answer: Yes, they may both apply nationally in any Member State (the same or different) and afterwards initiate a mutual recognition procedure if they intend to market the medicinal product in more than one Member State, unless they can be considered to be the same applicant (as defined in Question 8). It is not possible to start a mutual recognition procedure based on a marketing authorisation granted for a different applicant, even though the content of the dossier is the same.

Question 10
**Is it optional for a Company to submit a bibliographic application when there is an original/reference medicinal product to which essential similarity can be claimed, or is an application, in accordance with Article 10(1) or 10(3), the appropriate legal basis for such an application?**

**Answer:** According to Chapter 1 of Volume 2A of the Notice to Applicants, bibliographic applications may be submitted for any medicinal product (chemical or biological substance) if it can be demonstrated that the active substances of a medicinal product have been in well-established medicinal use within the Union for at least 10 years, with recognised efficacy and an acceptable level of safety.

The CMDh recommends that applications in accordance with Article 10(a), Directive 2001/83/EC, be only submitted when there is no reference/medicinal product to which essential similarity can be claimed.

As for other applications, the MRP or DCP is compulsory for bibliographical applications intended for authorisation in more than one MS (where the centralised procedure is neither mandatory nor chosen by the Applicant).

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**COMBINATION PACKAGES**

**Question 11**

**What is the definition of a Combination Package? Is it possible to apply for Combination Packages through MRP or DCP?**

**Answer:** There is no definition of a combination package in Directive 2001/83/EC, but the CMDh has agreed on the following understanding of a combination package: A combination package is a package, which contains more than one medicinal product marketed under a single tradename, and intended to be used in a medical treatment where the individual medicinal products are simultaneously or sequentially administered. The combination packages should be distinguished from a fixed combination which is a combination of active substances within a single pharmaceutical form.

The medical tradition of using combination packages is different among the EEA Member States. However, most of the Member States have accepted combination packages for some medicinal products including vaccines and some HRT products. If a combination package is accepted, it is considered as a unique product with its own marketing authorisation and the holder of the marketing authorisation has the full legal responsibility for the product. In principle, many Member States could accept a combination package if there are strong arguments for the provision of a combination package with respect to benefit to public health or where the use of a combination package is more user friendly for the patient or healthcare professional. Commercial reasons are not considered a valid justification for the provision of a combination package. Due to the different medical traditions among Member States, CMDh advice to applicants is to consult with the RMS well in advance of any future MR or DC procedure in order to clarify the acceptance of the combination package in the relevant MSs.
MANUFACTURING SITES RESTRICTED TO PARTICULAR MEMBER STATES IN THE MRP AND DCP

Question 12

Is it possible in a MRP/DCP to register a manufacturing site or batch release site for a limited number of Member States (i.e. not all MSs included in the procedure)?

Answer: Manufacturing sites and batch release sites approved via the MRP/DCP are considered approved for all MSs included in the procedure. Even though not all manufacturing sites are necessarily intended for use in all MSs included in the procedure, it is not necessary to specify in the application form which site applies to which MS.

It is not possible to delete manufacturing sites for medicinal products authorised via the MRP/DCP on a national basis. The MRP variation procedure should be followed, as all manufacturing sites for a MRP/DCP apply to all MSs involved in the procedure.

With regard to the identification in the package leaflet (PL) of the manufacturer responsible for batch release in the EEA, the locally printed PL in each MS needs only to include the manufacturing site specific to that MS. The change of this information only in the PL approved by a MS will be managed at the national level.

CHANGE IN THE NAME OF A MEDICINAL PRODUCT PRIOR TO GRANTING A MARKETING AUTHORISATION

Question 13

How should a change in the name of a medicinal product between finalisation of a MRP or DCP and prior to granting a national marketing authorisation, be handled?

Answer: It should be discussed with the particular Member State whether or not the change in the name of the medicinal product can be handled as part of the national implementation process. If this is the case, then MAHs are reminded that the mutually recognised English Package Leaflet should be updated e.g. in parallel with the next regulatory submission. If the change in the name of the medicinal product cannot be handled as part of the national implementation process a MRP variation should be submitted.

POST-APPROVAL COMMITMENTS

Question 14

Is it possible to have post-approval commitments in MRP/DCP?

Answer: There is no specific provision or specific procedure for post-approval commitments in Directive 2001/83/EC.

Proposals from applicants to submit additional data after the approval of a marketing authorisation, variation or renewal should not (by definition) impact the risk/benefit decision on the application under consideration and should only be made in exceptional circumstances. Any such data should be submitted by variation in the normal manner using
an appropriate variation category. The variation will be processed according to the standard procedure for the relevant variation type. Since the approval of the marketing authorisation, variation or renewal is not contingent on additional data, they should not be associated with commitments not to market the product prior to the submission of the additional data.

There are some standard commitments relating primarily to Module 3 of the dossier, the basis for which is clearly described in European guidelines, for example a commitment to perform confirmatory stability studies on production-scale batches, where stability data for pilot-scale batches has been accepted during an application for a marketing authorisation, as being sufficient to justify the proposed shelf-life and storage conditions. Such standard commitments should not normally require the submission of the additional confirmatory data to the Competent Authorities and hence no variation application would be required. The MAH is responsible for ensuring that the commitment is fulfilled after product approval. It is expected that the MAH will inform the RMS should any issues arise during the confirmatory studies (e.g. any confirmed out of specification results obtained during the confirmatory stability studies should be reported).

**Question 14.a**

*In order to receive a positive decision on Day 90/210, is it acceptable to propose to withhold the marketing of the product until further data have been generated in order to resolve deficiencies identified in safety, quality or efficacy data submitted in the application?*

**Answer:** A marketing authorisation may be approved after satisfactory evidence of safety, quality and efficacy have been provided such that the benefit / risk evaluation for the product is positive. A proposal to withhold a proposed medicinal product from marketing until further data are available indicates that the evidence supporting the application is incomplete and the marketing authorisation may not be approvable. It is not acceptable to conclude MRP/DCP with a commitment to withhold the product from the market in order to generate additional data necessary to demonstrate that the safety, quality or efficacy of the medicinal product is satisfactory.

**PROCEDURE NUMBER AFTER SWITCH OF RMS**

**Question 15**

*If there is a change of the RMS, should the type of authorisation procedure be changed in the new procedure number?*

**Answer:** No, the procedure number allocated by the new RMS after a switch of the RMS should maintain the reference to the type of authorisation procedure of the medicinal product in the EU (MR/DC). Although the complete numbering (including the ending MR/DC element) will not be used in the subsequent post authorisation procedures (i.e. variations, renewals, etc.), the new assigned number will maintain its reference in order to be consistent to the former EU
number and also to assure the traceability of the procedure in the national databases, when applicable.
This Q&A is applicable from the date of publication; there is no need for subsequent corrections of previously issued numbers.
For example:
MRP:
Former EU number: DK/H/xxxx/001/MR
New EU number: ES/H/yyyy/001/MR
DCP:
Former EU number: DK/H/xxxx/001/DC
New EU number: ES/H/yyyy/001/DC

INFORMATION BY MARKETING AUTHORISATION HOLDERS ON ACTIVE SUBSTANCE INTERMEDIATE MANUFACTURERS

Question 16

What level of details should be provided for active substance manufacturers on application forms for new marketing authorisations, variations and renewals?

Answer: Names and addresses of all sites involved in the manufacture of the active substance from the first use of the designated active substance starting materials should be provided. This includes intermediate manufacturers, quality control sites and in-process testing sites and is irrespective of the means by which the data requirements for the active substance are met – by either EDQM Certificate of Suitability (CEP), Active Substance Master File (ASMF) or full details in the dossier. For CEPs, also sites not openly declared on the CEP should be provided. Any sites not applied for are considered to be non-approved. Subsequent changes to the information provided would also trigger a need for a variation application.

GMP CERTIFICATES AND QP DECLARATIONS

Question 17

Can a member state invalidate a procedure because a GMP certificate was not provided for an API for which the QP declaration was provided?

Answer: No. A satisfactory QP Declaration is always necessary and is normally sufficient to confirm that the manufacture of active pharmaceutical ingredients (APIs) comply with
Good Manufacturing Practice (GMP), as required by Article 8 Paragraph 3 (ha) of Directive 2001/83/EC.

Supplementary information may be attached to the QP declaration to support a risk-based approach by the manufacturer in establishing priorities for its own audit programme. For example, results of inspection report(s) or GMP certificate(s) issued by EEA, Mutual Recognition Agreement (MRA) partners or other recognised authority together with other supporting information may also be submitted.