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CMDh SOP on decision-making process for new active substance status or extension of marketing protection or data exclusivity

1. Introduction

In some cases of marketing authorization applications (MAA) or variations questions on specific issues may arise that have a significant impact on future applications for other medicinal products. These specific cases are described in Chapter 1 of NtA Vol. 2A for MAAs containing a new active substance (NAS) as well for applications requesting an additional year of marketing protection according to Art. 10(1) par. 4 of Dir. 2001/83/EC or an additional year of data exclusivity according to Art. 10 (5) or, resp., one year of data protection according to Art. 74a of Dir. 2001/83/EC as follows:

"...

If a medicinal product applied for contains a modification of an existing substance and belongs to the same applicant/marketing authorisation holder, it should be clarified during the marketing authorisation procedure whether the product contains a new active substance or not. This clarification impacts on the existence or not of a global marketing authorisation. This assessment is to be done in accordance with the criteria of Annex I at the end of this Chapter 1 of NtA Vol. 2A and the conclusion should be reflected in the assessment report. If the assessment report does not indicate that the product contains a new active substance, it will be considered that the product at stake contains the same active substance and belongs to the global marketing authorisation....

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In accordance with the fourth subparagraph of Article 10(1) of Directive 2001/83/EC, the ten year period of marketing protection may be extended by one year in the event of authorisation of new therapeutic indications representing a significant clinical benefit in comparison with existing therapies. The additional year of marketing protection applies to the global marketing authorisation for the reference medicinal product. Generic products, with or without the new therapeutic indication, may not be placed on the market until expiry of the eleventh year.

Every application for a new indication must be assessed by the competent authority to determine whether the new therapeutic indication brings a significant clinical benefit in comparison with existing therapies. In the case of products authorised in accordance with Regulation (EC) No 726/2004, Commission decisions authorizing new therapeutic indications will contain a clear statement of whether

the new indication represents a significant clinical benefit in comparison with existing therapies. In the case of medicinal products authorised through the decentralised or mutual recognition procedures, the assessment report by the reference Member State will contain a clear statement of whether the new indication represents a significant clinical benefit in comparison with existing therapies...

...

...Article 10(5) of Directive 2001/83/EC reads: "In addition to the provisions laid down in paragraph 1, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity will be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication." The data exclusivity period is non-cumulative to other periods of protection: it refers exclusively to the data concerning the new indications.

Every application for a new indication must be assessed by the competent authority to determine whether the new indication for a well-established substance is based on significant pre-clinical or clinical studies. In the case of products authorised in accordance with Regulation (EC) No 726/2004, Commission decisions authorizing new therapeutic indications for well-established substances will contain a clear statement of whether the new indication is based on significant preclinical or clinical studies. In the case of medicinal products authorised through the decentralised or mutual recognition procedures, the assessment report by the reference Member State will contain a clear statement of whether the new indication is based on significant preclinical or clinical studies...

...

Article 74a of Directive 2001/83/EC reads: "Where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised."

When adopting a decision authorising a change of classification of a medicinal product, the competent authority must assess whether the change is based on significant preclinical tests or clinical trials. In the case of products authorised in accordance with Regulation (EC) No 726/2004, Commission decisions authorising a change of classification will contain a clear statement of whether the change is based on significant preclinical tests or clinical trials. In the case of medicinal products authorised by the Member States, the decision of each competent authority authorising the change will contain a clear statement of whether the change is based on significant preclinical tests or clinical trials."

In cases of centralised MAA according to Regulation 726/2004/EC these decisions are automatically taken by all European Member States. However, in cases of decentralised /mutual recognition (indicated in this document as national applications/procedures) the procedures in which these decisions are taken may not involve all MS. The impact of decisions concerning new indications on the marketing protection period mentioned in article 10(1) first paragraph plus the one year data exclusivity period mentioned in article 10(5) or one year of data protection according to article 74a is relevant to all European Member States. Proposals for approval of a non-cumulative period of data exclusivity under Article 10.5 or for extension of the ten-year period referred under Article 10.1 or one year of data protection under Art. 74a should be discussed in the CMDh so that all European Member States are informed of the proposal and have opportunity to comment on the NCA recommendation.

[It should be noted that for the granting of an additional year of data exclusivity acc. to Art. 10\(5\) the term "new indication" is to be interpreted literally, i.e. the indication must not be approved for the](#)

same active substance within the EU before. The "new indication" in this case is therefore substance-related. Instead, for the additional year of market protection according to Art. 10(1) the new indication should bring a significant clinical benefit in comparison with existing therapies. This significant benefit can therefore also be product-related.

The objective of this SOP ~~is, therefore, to~~ is to ensure that the relevant competent authority (having received a national application) immediately after receipt of such an application informs the CMDh, presents the background and assessment of these applications in the next plenary meeting e.g. after circulation of the PVAR, leads a discussion and final voting on the NAS status or additional year of marketing protection or data exclusivity and considers the majority vote on these specifics in his final decision.

The discussion and the final voting of the CMDh on the matter is based on Article 27 (1) a. in connection with Article 27 (6) of Directive 2001/83/EC which reads

"Save where otherwise provided for in this Directive, the Member States represented within the coordination group shall use their best endeavours to reach a position by consensus on the action to be taken. If such a consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall prevail."

This SOP is applicable to applications received in decentralised and mutual recognition procedures. MS have agreed to adapt to these procedures for purely national marketing authorisations as well and any trend vote in CMDh should be considered by national competent authorities.

2. Information of the CMDh and discussion

The NCA that receives a national application for a new active substance (NAS) or any application for nationally authorised products according to Articles 10(1) or 10(5) or a change in the classification of the medicinal product according to article 74a of the Directive 2001/83/EC informs the CMDh immediately after receipt of these applications in the next CMDh meeting to make all European Member States aware of these application applications.

The relevant NCA presents its preliminary assessment of the respective application in the following plenary meeting of the CMDh. A precise rationale for the first recommendation should be given. A discussion on the issue should then take place between all member states. If a member state discovers that a new indication for which data exclusivity is applied for in accordance with article 10(5) is already approved in this member state, and the assessing NCA has not taken this into account in the preliminary assessment, the member state should notify the assessing NCA at this stage.

In this meeting there will be no final decision on the status of the products applied for. This meeting is meant for discussion and exchange of opinions and comprehensive information. It is also to be expected that a draft recommendation by the lead competent authority may not be possible at this stage as the data submitted by the applicant might not be complete. The draft recommendation on NAS status or extension of marketing protection or data exclusivity may be postponed to a later stage after receipt of the applicant's response document in the clock stop phase. The relevant competent authority should forward all comments raised during the discussion in CMDh to the applicant/MAH.

The next CMDh discussion in this respect should take place after circulation of the draft assessment report/draft FVAR. A decision on the application should be proposed here at the latest as there will be no further opportunity for the applicant to submit any new study data etc. Therefore, at this stage all member states in CMDh should be asked what position they are likely to take on the draft recommendation (trend voting). If the trend vote is negative with regard to a status as NAS or

concerning the additional year of marketing protection or data exclusivity, the applicant should be informed accordingly by the relevant competent authority and given the opportunity to present his position in an oral explanation in the further course of the procedure.

After this oral explanation or, if this is not requested by the applicant⁷, before finalisation of the procedure a final voting in CMDh should take place according to the CMDh Rules of Procedure (<http://www.hma.eu/205.html>)-<http://www.hma.eu/205.html>).

The outcome of the voting will be published in the CMDh minutes. In case there is no consensus on the proposed decision after the voting of the CMDh the member states in the minority will be mentioned in the minutes.

3. Outcome

The lead competent authority should accept the outcome of the final voting.

The lead authority should inform the secretariat of CMDh of its final decision. The decision will be published in the CMDh minutes following approval of the marketing authorisation/variation. The outcome of a voting will also be published for purely nationally authorised products.

In relation to a change in the classification of the medicinal product according to article 74a, each competent authority will take its own decision as to whether the one-year data exclusivity is to be granted. The RMS assessment presented at the CMDh should therefore be seen as a guidance that NCAs should take into consideration and make their best endeavours to follow.

In case there is a disagreement (on the application itself) at the end of procedure (independent from the claim for NAS or the additional year of marketing protection or data exclusivity) which leads to a referral to the CMDh and CHMP, the publication of the outcome on the status should be postponed until a final decision by a consensus in the CMDh referral or, in case of a CHMP referral, a Commission Decision is taken. A divergent decision related to marketing protection or data exclusivity, or NAS status is not a potential serious risk to public health.

