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PUBLIC CONSULTATION PAPER

Recommendation on

"Pharmacovigilance Urgent Measures"

procedure under Article 107 of Directive 2001/83/EC

DG Enterprise and Industry wishes to consult stakeholders on the guideline concerning Recommendation on "Pharmacovigilance Urgent Measures" procedure under Article 107 of Directive 2001/83/EC, with a view to the incorporation of the guidance in Volume 9A in Eudralex.

Contributions should be sent by e-mail to entr-pharmaceuticals@ec.europa.eu **by 3 April 2009.**

Contributions will be made publicly available on the 'Pharmaceuticals' website[1] of the Commission once the consultation period is over, unless a specific request for confidentiality is made, in which case only an indication of the contributor will be disclosed. If you do not wish your contribution to be made public, please clearly indicate so.

This document does not represent an official position of the European Commission. It is a tool to explore the views of interested parties.

[1] http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/new_en.htm

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Recommendation on "Pharmacovigilance Urgent Measures" procedure under Article 107 of Directive 2001/83/EC

INTRODUCTION

Article 107 of Directive 2001/83/EC as amended by Directive 2004/27/EC, states that:

"1. Where, as a result of the evaluation of pharmacovigilance data, a Member State considers that a marketing authorisation should be suspended, revoked or varied in accordance with the guidelines referred to in Article 106(1), it shall forthwith inform the Agency, the other Member States and the marketing authorisation holder.

2. Where urgent action to protect public health is necessary, the Member State concerned may suspend the marketing authorisation of a medicinal product, provided that the Agency, the Commission and the other Member States are informed no later than the following working day.

When the Agency is informed in accordance with paragraph 1 in relation to suspensions and revocation, or the first subparagraph of this paragraph, the Committee shall prepare an opinion within a timeframe to be determined depending on the urgency of the matter. In relation to variations, the Committee may upon request from a Member State prepare an opinion.

Acting on the basis of this opinion, the Commission may request all Member States in which the product is being marketed to take temporary measures immediately.

The final measures shall be adopted in accordance to the procedure referred to in Article 121(3)."

Therefore it introduces the obligation for the CHMP to adopt an opinion in case the suspension or revocation of a national marketing authorisation in a MS is being considered based on the evaluation of pharmacovigilance data. This procedure only applies to products already authorised; applications for MA are not concerned.

The same Article also introduces the possibility for a MS to request the Opinion of the CHMP when a variation is being considered based on the evaluation of pharmacovigilance data.

This reflection paper describes the specific conditions under which this procedure may be started or triggered.

It also includes a general description of the procedural aspects for the handling of this procedure by the EMEA/CHMP. These procedural elements are similar and based on the ones already existing for referrals.

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▪ ***Who should notify?***

"Where, as a result of the evaluation of pharmacovigilance data, a Member State considers that a marketing authorisation should be suspended, revoked or varied in accordance with the guidelines referred to in Article 106(1), it shall forthwith inform the Agency, the other Member States and the marketing authorisation holder."

It should be noted that in any case (revocation, suspension, variation) the MS(s) should inform the EMEA, the other MSs and the MAH before any regulatory action is taken. However, where a MS suspends the authorisation of a nationally authorised product in order to urgently protect public health in its territory, the MS should inform the Agency, the EC and the other MSs no later than the following working day (see also Notice to Applicants, volume 9 A, part II, section 1.7 – Overall Pharmacovigilance Evaluation and Safety Related Regulatory Action).

The **Rapid Alert system should be used** to inform the other Member States, the Agency and the European Commission in this regard (for further guidance on the criteria for Rapid Alert please refer to Notice to Applicants, Volume 9A, part II, section 4 – Rapid Alert and Non-Urgent Information in Pharmacovigilance).

In any case (suspension, revocation or variation), when circulating the information through the Rapid Alert system, the Member State should clearly confirm that a procedure under Article 107 is being notified and, in the case of variations, whether a CHMP Opinion on the issue is being requested. In addition, the MS should confirm that action is being considered after evaluation of pharmacovigilance data as defined in this Reflection Paper. The MS should copy the Rapid Alert to the CHMP secretariat.

▪ ***Start of an Article 107 procedure – In which situation?***

A procedure leading to the adoption of a CHMP Opinion will start in the following cases:

Revocation/Suspension: When a Member State is considering the suspension or revocation of the Marketing Authorisation(s) for (a) medicinal product(s) authorised in its territory (non-centrally authorised products only) as a result of the evaluation of pharmacovigilance data.

In case of suspension or revocation the following scenarios can be considered:

1. Action taken by Member State(s)
   The National Competent Authority(ies) of the MS(s) as a result of the evaluation of pharmacovigilance data decide(s) on the suspension or revocation of the MA(s).

2. Action taken by Marketing Authorisation Holder(s)
   The MAH(s) decide(s) to voluntarily suspend the marketing of the medicinal product(s) or withdraw the MA(s).
   - When action is taken in agreement with the NCA(s) (following the assessment by such NCA(s) and consideration of the suspension or revocation of the MA(s)) it falls within the scope of Article 107. This needs to be made clear by the MS(s) when notifying the procedure.
   - When the voluntary suspension or withdrawal is purely made on the basis of the MAH(s) own initiative this is considered outside the scope of Article 107. In this context, based on any pharmacovigilance information provided by the MAH(s) a MS can however trigger an Article 107 procedure.

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Variation: Upon request from a Member State as a result of the evaluation of pharmacovigilance data. The procedure can be initiated by the MS(s) which is (are) considering the variation of the concerned product(s).

In case of variations, the following situations could be considered by a MS when applying an Article 107 procedure (criteria for Rapid Alert, Notice to Applicants, Volume 9A, part II, section 4 – Rapid Alert and Non-Urgent Information in Pharmacovigilance):

- Introduction of new contraindications;
- Introduction of new warnings;
- Reduction in the recommended dose;
- Restriction of the indications;
- Restriction in the availability of a medicinal product.

In order to provide for a consistent approach on the application of this procedure, pharmacovigilance data in this context is understood as any emerging information on the safety of a medicinal product regardless of its origin, e.g. expedited reports, periodic safety update reports, scientific literature, clinical trials, epidemiological studies, and post-authorisation safety studies which have been evaluated by the Member State(s).

In principle, regulatory actions following benefit/risk assessments in which no emerging pharmacovigilance data as defined above have been considered should not trigger an Article 107 procedure.

In case of a variation, suspension or revocation of a medicinal product authorised through the mutual recognition or decentralised procedures, resulted from evaluation of pharmacovigilance data, Article 107 should be used instead of triggering an Article 36 referral procedure.

- ***When should the MS(s) inform?***

The Member State(s) shall inform the Agency, the other Member States and the Marketing Authorisation Holder of its intention to suspend, revoke or vary the Marketing Authorisation(s) of (a) medicinal product(s) authorised in its territory as a result of the evaluation of pharmacovigilance data. In principle, Member State(s) shall not take any regulatory action before informing these parties.

However, where urgent action is considered necessary to protect public health the MS concerned may suspend the MA of a medicinal product provided that the Agency, the Commission and the other MSs are informed no later than the following working day.

- ***What is the scope of the procedure?***

The CHMP is called upon to issue an opinion on a specific matter where a Member State is considering the suspension, revocation or variation of a Marketing Authorisation based on emerging pharmacovigilance data. In principle the scope of the procedure is limited to the issues identified by the Member State(s).
Given that pharmacovigilance evaluations are frequently conducted on drug substances rather than on individual medicinal products and in the interests of public health protection, a notification under Article 107 and the subsequent CHMP opinion(s) may relate to an individual medicinal product or a range of medicinal products containing the same active substance. This should be made clear by the Member State(s) when notifying the Agency of an Article 107.

- ***Which Member States are concerned?***

All Member States with MA(s) for the medicinal product, or medicinal products containing the active substance(s) are concerned by the procedure and will therefore be covered in the CHMP Opinion and subsequent Commission Decision.

Upon receipt of the Rapid Alert notifying of an Article 107 procedure the EMEA will request MSs to identify all concerned products within a specified timeframe. MAs not identified by the MSs within such timeframe will not be included in the procedure.

- ***Procedural elements***

According to legislation the aim of this provision is to allow for measures to be taken in a short timeframe:
"…the Committee shall prepare an opinion within a timeframe to be determined depending on the urgency of the matter…
Acting on the basis of this opinion, the Commission may request all Member States in which the product is being marketed to take temporary measures immediately."
When adopting an Opinion, the CHMP will indicate in this Opinion whether temporary measures are needed and the urgency of such measures. This CHMP recommendation will be the basis for the EC to request temporary measures (if needed) to be taken by all MSs in which the product has a Marketing Authorisation.

Start of procedure
The procedure at CHMP level starts following notification by the Member State(s).

Timeframe
The Committee shall prepare an **opinion within a timeframe to be determined depending on the urgency of the matter.** Therefore the timeframe applicable will be decided by the CHMP on a case-by-case basis.
Data to be reviewed by the CHMP
A Rapid Alert from (a) Member State(s) notifying an Article 107 procedure should always be accompanied by an Assessment Report prepared by such Member State(s) and any other relevant documentation which should then be made immediately available by the EMEA to all CHMP members. The Member State(s) notifying the procedure should also make this information available to the concerned MAH(s) in its (their) own territory. The EMEA will request all MSs to identify, in a very short timeframe, the concerned MAH(s) in their territory. Once the MAH(s) in the EU MSs have been identified the EMEA will immediately send them the Assessment Report of the triggering MS(s). All other NCAs should also supply the EMEA with any other information relevant to the matter in question in a short timeframe. The EMEA will circulate such information to all CHMP members.
Article 107 does not provide details on the procedures leading to the adoption of an Opinion and on the possibility for MAHs to provide written and/or oral explanations. Although all reasonable efforts should be made to hear (in writing and/or orally) the MAH(s), there could be circumstances where in order to protect public health the CHMP will decide to adopt an Opinion immediately or in a very short timeframe and therefore the CHMP may agree not to hear the MAH(s) concerned or to only hear the brand leader. This decision will be made by the CHMP on a case-by-case basis. In the case when the CHMP doesn't consider that there is a need to immediately adopt an Opinion, the MAH(s) will in principle be given the opportunity to comment on the Assessment Reports of the triggering MS(s) and/or provide answers to a CHMP List of Questions.

Organisation of the work within the CHMP

Normally, in order to consider the matter the CHMP should appoint a Rapporteur and one or more Co-Rapporteur(s) (the general principles to be considered in the appointment of Rapporteurs are established in the paper on "CHMP Rapporteur/Co-Rapporteur appointment – EMEA/124066/2005).
However, when the timeframe does not allow for the (Co-) Rapporteur(s) to be appointed in accordance with the above procedure, the CHMP chairman appoints a Rapporteur and Co-Rapporteur(s) on an ad-hoc basis.
Considering the urgency of the matter it can be necessary to agree on a timetable by written procedure. In exceptional cases a CHMP Extraordinary meeting can be organised.

CHMP Opinion
Taking into account the pharmacovigilance basis of this procedure and the need to have a CHMP Opinion in a short timeframe, such Opinion will only include the scientific conclusions - as opposed to the usual Opinion, which includes all the Product Information related annexes. However, if in its scientific conclusions the CHMP recommends that there is a need to introduce changes to the Product Information (for example a warning should be included), the specific wording should be agreed by the CHMP and clearly reflected in the Opinion.
In principle, the CHMP Opinion will cover the medicinal product or the range of medicinal products containing the same active substance as identified by the Member State(s) notifying the Article 107 procedure. However, in its scientific recommendation the CHMP can indicate that the measures being proposed are also appropriate in relation to other medicinal products/active substances. In this case, i.e. if in its Opinion the CHMP recommends that measures are required for a broader scope of products the CHMP may recommend to the European Commission to trigger an Article 31 referral if it considered that this is of Community interest (justification to be clearly stated in the CHMP Opinion).
In case more than one notification for a procedure under Article 107 has been received from MSs in relation to the same medicinal product(s)/active substance on the basis of the same emerging pharmacovigilance data, the CHMP will only adopt a single Opinion.

The CHMP adopts an Opinion recommending that:
1) Measures are needed

Measures should be proportionate to the health risk and may include any of the following recommendations:

- Relevant sections of the Summary of Product Characteristics, Labelling and Package Leaflet should be amended and/or the marketing authorisation should be maintained provided that certain conditions should be fulfilled. In case of such conditions, the follow-up should normally be undertaken at Member State level, save in exceptional circumstances where this can be done at CHMP level (this needs to be duly justified in the CHMP opinion).
- MA(s) should be suspended

  The recommendation for a suspension should normally be linked to conditions whose fulfilment could lead to the lifting of the suspension. The CHMP will identify such conditions in its Opinion. The subsequent assessment of the conditions for lifting the suspension should normally be undertaken at Member State level, save in exceptional circumstances where this can be done at CHMP level (this needs to be duly justified in the CHMP Opinion).
- MA(s) should be revoked

When the CHMP considers that urgent measures are needed it should also recommend in its Opinion the **need or not for the Commission to adopt temporary measures** to be taken immediately.

The CHMP can also indicate in its Opinion if in addition to the specific measures there is also a need for follow-up or further actions to be considered (for example, to recommend to the European Commission to trigger a referral procedure under Article 31 of Directive 2001/83/EC in case the CHMP considers there is Community interest in performing a thorough re-evaluation of the benefit-risk of the products concerned).
2) No measures are considered necessary and no further follow up action is recommended.
3) No measures are considered necessary but the CHMP recommends that further actions could be taken. In certain cases the CHMP could be of the opinion that the issue does not require urgent measures to be taken but should be further evaluated at Community level and therefore the European Commission should be asked to trigger a referral procedure under Article 31 of Directive 2001/83/EC, as amended. In such case the Community interest as well as a clear justification needs to be clearly stated in the CHMP Opinion.
Once the CHMP has adopted its Opinion, the EMEA immediately informs the EC.
No re-examination of the CHMP Opinion is foreseen.
On the basis of this Opinion, the Commission may request all Member States in which the product has a Marketing Authorisation to take temporary measures immediately. The temporary measures will be a Commission decision and will be legally binding on the Member States.
Final measures will be adopted in accordance with the procedure referred to in Article 121(3) (Standing Committee procedure).

Publication
Transparency measures will be developed along the policy applied for Article 31 referrals i.e.

<u>At start of procedure</u>
Information on the MS(s) triggering the procedure and the reasons will be made public.

<u>CHMP Opinion</u>
The CHMP recommendation including the need for temporary measures will be made public.

<u>At Commission Decision</u>
Full scientific opinion will be made public.