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EMA/CMDh/416275/2010
Patient Health Protection

CMDh and PhVWP Best Practice Guide on communication and implementation of safety information

1. Introduction

A Joint Working Group (JWG) between the CMDh and PhVWP was set up in March 2006 to discuss issues of common interest. The CMDh and PhVWP have regular scheduled monthly meetings in parallel at the European Medicines Agency and the JWG usually meets every second month.

Communication between the groups is facilitated by two (2) appointed delegates from each group. One of the delegates representing the presidency appointed for a period of six months; the second delegate appointed for one (1) year. The representatives will be appointed by each group according to their respective internal procedures.

Information and feedback from the representatives should appear as a permanent item in the meeting agendas for both groups.

The PhVWP has a mandate to provide advice on the safety of medicinal products authorised in the European Union to its stakeholders, i.e. the CHMP/European Medicines Agency and the National Competent Authorities (NCAs). As issues arise these are communicated to CMDh in order that pharmacovigilance recommendations can be implemented in Marketing Authorisations (MAs) in a coordinated manner so that European patients can receive important safety information at the same time. Where appropriate, the PhVWP will request expert advice from CMDh concerning regulatory procedures and decisions, and the CMDh will request expert advice from the PhVWP regarding pharmacovigilance issues.

Product related safety issues which result in a recommendation to amend the Summary of Product Characteristics (SmPC) and/or Package Leaflet (PL) should be implemented in concerned MSs by variation procedures in a harmonised way. This may concern products containing a particular active ingredient or a class of products authorised through MRP/DCP and/or purely national procedures. With the implementation of Commission Regulation 1234/2008 implementation of agreed European safety updates for MRP/DCP products will usually follow a Type IB (C.I.3) procedure. Where the same change affects a class of products and more than one MA held by an MAH worksharing may be agreed with CMDh.

This aim of this paper is to raise awareness of pharmacovigilance recommendations and to provide practical procedural guidance to Member States (MSs) on the harmonised implementation procedure

2. Legal considerations

The recommendations made by the PhVWP are not legally binding decisions but reflect the outcome of scientific assessment and discussions between MSs, resulting in clear and specific recommendations. To achieve or maintain harmonisation of SmPCs and package leaflets the aim is to have the recommendations implemented in a consistent way and a timely manner. Some implementation exercises may also result from Referral procedures, and in these cases MAHs would be obliged to implement the updates.

3. Exchange of information on outcome of PhVWP discussions and recommendations

To inform CMDh of the issue and discussions and to facilitate implementation, a written report should be circulated to the CMDh for each safety update:

- For MRP/DCP products: when the changes affect more than one MA held by a MAH, different MAHs or when there are generic MRPs/DCPs
- For purely nationally authorised products: when the changes affect a class of products and when communication is included in the Monthly Report ¹
- Any other safety issue that is considered on a case by case basis to be sufficiently important

The PhVWP secretariat will send the report to the secretariat for CMDh who will circulate the report to CMDh without delay. The report will be added to the next CMDh meeting agenda.

The PhVWP Report to CMDh should follow the template given in Annex I. The following should be described in the report:

1. the safety issue (background)
2. a summary of the PhVWP assessment
3. the documents that have been assessed
4. the outcome of the PhVWP assessment
5. a table of active substances or products included in the assessment
6. the conclusions and recommendations including the agreed text or key elements for the SmPC and PL
7. a communication plan when appropriate
8. a plan for the implementation including a time table and follow-up of the procedure (see Section 6)

For products in MRP/DCP, the RMS has the responsibility to initiate and co-ordinate the implementation. For nationally authorised products, the NCAs are responsible for co-ordinating implementation in their respective MSs.

¹ This means that in the case of purely nationally authorised products (even with with generic MRPs/DCPs), MRPs/DCPs with a single MA and a single MAH would not routinely result in the production of a report

4. Interaction upon request of RMS or any other Member State

If agreement cannot be reached regarding relevant emerging safety issues, or safety issues arising during assessment of a new MA or variation procedure, or during development of guidance documents or work-sharing projects, a Member State may refer this to PhVWP and/or CMDh for consideration and advice. The Member State should make a written request and, following the template in Annex II, describe the issue and questions to be addressed. This request should be sent to the CMDh and PhVWP secretariats. The outcome of the PhVWP/CMDh discussions should then be documented, using the report templates provided in Annexes I and III and sent to the CMDh and PhVWP secretariats for onward circulation to the respective groups.

5. Interaction upon request of PhVWP/CMDh

The PhVWP/CMDh may identify safety or regulatory issues for which CMDh/PhVWP advice is requested. Using the template in Annex II, the RMS/lead MS will request advice from the PhVWP/CMDh; such a request will include the safety or regulatory issue and questions to be addressed. The outcome of the PhVWP/CMDh discussion will be documented using the templates in Annexes I and III.

6. Timetables for implementation

The implementation timetable proposed in the PhVWP report (see Section 3) should be agreed by PhVWP and CMDh before initiation of the exercise. The specific timetables will be dependant on the safety issue concerned and in some cases it may be necessary to expedite the introduction of new PLs into production batches. Before confirming the timetable it should be checked whether, for practical purposes, the implementation could be combined with any other ongoing regulatory action (e.g. Article 30 or 31 Referrals or introduction of a new Core Safety Profile resulting from PSUR work sharing). However, depending on the public health implications it may be preferable to implement the safety issue immediately and not combine it with other regulatory actions.

Usually on agreement of the timetable the NCAs should be given one month to prepare their communications to MAHs, who will then be given a further month to prepare and submit the necessary variations. The NCAs would be allowed 2 months to process the applications, which would allow for validation and assessment of the Type IB procedure. See example timetable below:

Task	Deadline	Example Timetable
Variation applications requested through CMDh/NCAs	1 month after initiation of the implementation plan.	31 January
Variation applications submitted by MA holders		28th February
Variation applications approved by NCAs		30th April

7. CMDh, PhVWP and MS communication with MAHs

To facilitate the implementation of new safety information and to ensure the cooperation of MAHs, in updating product information, it is important to consult the relevant stakeholders before finalisation of the wording and implementation plan.

This may be achieved by written communication to stakeholders and/or face to face meetings at the Agency in the margins of the PhVWP and CMDh meetings. The PhVWP delegate for the lead MS should take the lead in the communication with stakeholders.

To avoid the need for MAHs to individually consult with patient/consumers groups, the advice of the EMA working group with patients and consumers (PCWP) may be sought for the proposed PL wordings or other communication documents intended for healthcare professionals, patients and the general public. Consultation of patients and consumer groups is proposed in the case of substantive changes to the PL for widely used classes of medicines and for significant changes to the information on medicines used to treat rare diseases.

When consulting patient/consumer organisations, the PhVWP should contact the PCWP using the template provided in EMEA/628805/2008 and reproduced in Annex IV. The draft request should be prepared by the lead MS.

Summary information on the background to the changes will be published in the PhVWP monthly report published on the EMA website. The proposed amendments to the SmPC/PL, including the plan for implementation of the amendment, will be published on the CMDh pages of the HMA website (www.hma.eu)

An example letter template for NCAs to use when requesting the updates is provided in Annex V.

It should be noted that this template is only applicable when the wording has been agreed by all interested parties and is to be implemented by the MAH without amendment and when the subsequent variations applications do not require supporting information. In other situations a Type II variation may be required and the template should be modified as appropriate.

To reduce the number of queries received from MAHs on particular updates it is also useful to provide a public question and answer document outlining the reasons for the regulatory action. An example document is provided in Annex VI. This is however, not exhaustive and additional Q&As should be included that are relevant to the particular issue that would assist MAHs in understanding. The PhVWP (lead MS) may propose Q&As in the report of the issue that can be included on the CMDh website. Individual Member States may adapt this for their own National website.

8. Processing of European Procedure applications

If the wording for the SmPC and PL has been agreed by all interested parties and is to be implemented by the MAH without amendment, the subsequent Type IB (C.I.3) variation applications do not require supporting information and should be accepted by Member States Competent Authorities without further assessment or amendment. The RMS takes responsibility on behalf of CMS to request the variation from the MA holder and initiate and finalise the procedure. For Nationally authorised products Competent Authorities should follow the agreed European timetable for implementation.

9. Annexes I-IV: Template

Annex I

<day month in word year>

Doc.Ref.: <to be inserted by PhVWP Secr> **CONFIDENTIAL**

Patient Health Protection

Draft # <number> / Final <delete as appropriate>

PhVWP Report on<INN (product name if appropriate)>
and <safety issue> [*the title should be consistent with the
Agenda*]

Provided to the CMDh on behalf of National Competent Authorities

Agreed by the PhVWP in <month year>

PhVWP Representative:

Safety concern & background

<Description how issue arose, when PhVWP was informed first time and reason for evaluation at this point in time, or when last discussed by the PhVWP in case of follow-up discussion, explain procedure and status of review, as appropriate, refer to references in Annex, if applicable>

<Brief description of the concern, e.g. adverse reaction signal, findings from epidemiological/clinical study>

Clinical setting

<Placing the risk in the context of the benefit, indication, prevalence/incidences of the disease, population exposure>

Important aspects of the substance/product

<Aspects relevant to the safety issue, if any, e.g. pharmacodynamic properties, pharmacokinetics, interactions>

Information on the data assessed

<E.g. quality, strengths and limitations of the data>

Outcome of the assessment

<Description of seriousness, statement on the suspected causal relationship, estimation of the frequency of the adverse reaction or reporting rates with estimated patient exposure, risk factors; overall recommendations for risk minimisation, e.g. including the proposals for amended SmPC and/or PL wording, a communication plan when appropriate, recall information, if applicable (e.g. pharmacy or

patient level, date of recall) and a plan for the implementation including a time-table and follow-up of the procedure>

Regulatory comments

<E.g. statement indicating the context in which the assessment has been conducted (national procedure/CHMP procedure/European consensus, timelines for implementation of regulatory action, schedule for follow-up action(s) by the Marketing Authorisation Holder/Competent Authority, if applicable>

Documents

[Can be copied from the Agenda, add any further documents circulated during the meeting.]

Follow-up

This report will be circulated to the CMDh <month year>. *Include if appropriate*: Feedback from <CMDh, MAH, Member States> will be provided to the PhVWP in <month year>.

Annex

[List of Annexes (e.g. the PhVWP Assessment Report.)]

Annex II

<day month in word year>

Doc.Ref.: <to be inserted by PhVWP Secr> **CONFIDENTIAL**

Patient Health Protection

<RMS/MS/PhVWP/CMDh> request for <CMDh/PhVWP>
discussion on <safety/regulatory issue >

<PhVWP/CMDh>representative:

[This request should be drafted by the PhVWP/CMDh representative of the RMS or Lead Member State and submitted to the PhVWP and CMDh no later than two weeks before the next PhVWP/CMDh meeting.]

Background

[Description of the issue and procedural context in which the issue has arisen. Include reference to relevant PhVWP/CMDh meeting(s) and insert extracts from minutes or ARs as appropriate.]

Nature of request

[State the questions to be addressed]

Timetable

[Specify a deadline for the transmission of the PhVWP/CMDh recommendations to the CMDh/PhVWP or a proposed time table as appropriate.]

Documents

[Documents relevant for the discussion at the PhVWP/CMDh. Please specify on each document if it is for information or discussion and when they will be available]

Annex III

<day month in word year>

Doc.Ref.: <to be inserted by PhVWP Secr> **CONFIDENTIAL**

Patient Health Protection

CMDh Report to PhVWP on <regulatory issue>

agreed by the CMDh in <month year>

CMDh representative:

Background

[Description how issue arose, when CMDh was informed first time, or when last discussed by the CMDh in case of follow-up discussion, explain procedure and status of review, as appropriate.]

Documents

[Can be copied from the Agenda, add any further documents circulated during the meeting.]

Discussion

[Summary of discussion, level of detail as necessary.]

Conclusions

[List conclusions and recommendations to the PhVWP.]

Follow-up

This report will be circulated to the PhVWP <month year>. *Include if appropriate*: Feedback from <PhVWP, MAH, Member States > will be provided to the CMDh in <month year>.

Annex

[List of Annexes, if any]

Annex IV

Template for consultation of patient and consumer organisations of the PCWP on issues related to information on medicines

1. Consulting Scientific Committee/Working Group

.....

2. Name of the product/therapeutic class (+ active substance)

.....

3. Deadline and contact person for the consultation

Comments should be sent by *(deadline)* to *(contact person's e-mail)* (cc: PCWP secretariat)

4. Summary of the issue

Include a short summary on what PCWP consultation is sought. Provide brief description of the medicine, the mode of action and its indication. Describe, the scientific background, as well as the procedural context in which the issue has arisen (e.g. requested by Competent Authority or in the context of a therapeutic class review aiming at optimising the information in the Package Leaflet). If relevant, indicate also how urgent is the need for information update

5. Message to be conveyed

Describe the message to be conveyed to the patients/public in the proposed text

.....

6. Proposed text

Include the proposed wording (if it is a revision of an already existing text, make sure that the previous/current text is also included; alternatively track changes on the previous wording could be used.)

If available, please attach full Package Leaflet, SmPC and Labelling (in a separate document).

.....

7. Specific questions to the Patient/Consumer Organisation(s)

If necessary, formulate questions in which specific input from PCWP is sought.

- Question a).....
- Question b).....
- Question c).....
- (add questions as necessary)

RESPONSE OF Patient/Consumer Organisation(s)

Organisation(s) responding

.....

General comments

.....

Comments on specific questions formulated in section 7

- Question a).....
- Question b).....
- Question c).....
- etc

Specific comments on the text *(please use track changes on the proposed text provided)*

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ANNEX V

Letter Template

Head of Regulatory Affairs

<Company Name>

<Company Address1>

<Company Address2>

Date

Dear Sir/Madam

Re: Implementation of Warnings <safety/regulatory issue> in All <product class>

We are writing to request that you submit a variation to your Marketing Authorisation(s) in order to update the warnings on <safety/regulatory issue> in line with European agreements.

Background

Following consideration of the available data relating to <safety/regulatory issue> and discussion at the Pharmacovigilance Working Party (PhVWP) and the Co-ordination Group for Mutual Recognition and Decentralised Products – human (CMDh), all Marketing Authorisation (MA) holders for <product class> throughout the European Union are being requested to submit Type IB (C.I.3) variations (or equivalent national procedures – see below) for relevant products to implement the final agreed texts. The attached wordings (*append as an Annex*) have been agreed by the PhVWP and have been the subject of consultation with MA holders for brand leader products <and industry bodies at EU level> and are to be implemented without amendment.

European procedures

The applications do not require supporting information and will be accepted by Member States Competent Authorities without further assessment or amendment. No assessment reports will be issued as the RMS will take responsibility for the assessment of the implementation of the final SmPC and PL text. *<With regard to PL wording, a consultation with patient groups has been organised via the EMEA, and further user-testing by individual MA holders will not be expected on this occasion.>*

National procedure

[Insert details of national procedures here]

Timetable

You should submit variations no later than <**deadline**>. We will determine the variations by <**NCA deadline**> at the latest.

Fees

[Include any information on national fees]

Yours faithfully

NCA Contact Person

ANNEX VI

Question & Answer template

Implementation of Warnings on <Safety/Regulatory Issue>

Questions and Answers

1. Why are we being asked to make these changes?

The reasons supporting the new warnings should be provided together with brief details of any clinical data. The seriousness of the safety issue should be discussed.

The wording has been agreed at an EU level in consultation with MA holders for brand leader products <and industry associations>. The timetable for implementation has also been agreed at European level to ensure that healthcare professionals, patients and their carers receive this important safety information as soon as possible.

2. Where can I find further information on the scientific basis for this regulatory action?

The PhVWP executive summary can be found at <http://www.hma.eu/25.html>

3. My products already contain similar but not identical wording to that requested in the SmPC and/or PL. Do I still have to submit a variation to include the requested text?

Yes – the PhVWP considered it important that all product information should reflect the latest available data and that the same wording should be implemented in each case. Existing wording in relation to <safety/regulatory issue> should be replaced.

4. Some of the wording requested is already present in the SmPC and/or PL and will be duplicated if I submit a variation. Should I delete the current text and replace it with that provided?

Existing warnings should be replaced with the agreed PhVWP wording.

5. I will not be able to incorporate the new wording into leaflets by the next reprint what should we do?

The revised wording should be included in the leaflets as soon as practical and no later than <final deadline>. Batches that do not include the new warnings should not be released for sale after this

date. These are important safety warnings being implemented across Europe and patients should receive the appropriate safety information as soon as possible.

6. I do not have enough space in my PL to include the additional wording, please advise.

You will need to ensure that the leaflet you propose for the market accommodates the new wordings in a clear and legible manner. You may need to consider a revised format or a move to a booklet version to achieve this.

7. Please can I include other minor changes with this variation?

No other changes should be submitted at this time. If you consider that other changes are necessary as a result of the new wording please contact the Reference Member State or National Competent Authority to agree the changes before submission.