Federal Agency for Medicines and Health Products

Departments
Pharmacovigilance
and **Proper Use of Medicines**

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Circular 532

To marketing authorisation or registration holders
of medicinal products for human use
and veterinary use

SUBJECT **Risk management programs – Approval of "additional risk minimisation activities" by the national authorities**

This document is a translation of the official and signed versions in Dutch and French

Dear Madam, Dear Sir,

This circular pursues two goals. Firstly, it seemed useful to me to remind you of some obligations related to the **practical implementation** of the risk management programs (RMP) concerning medicinal products. Secondly, you'll find hereinafter useful information concerning the procedure followed by the Federal Agency for Medicines and Health Products (FAMHP) for the approval of the documents, materials and other measures that are provided in a RMP and this prior to their actual implementation.

1. Preamble

This circular specifically concerns the **additional** risk minimisation **activities**[1] (or *'non-routine risk minimisation activities'* described in a risk minimisation plan). The routine activities in pharmacovigilance, including the routine risk minimisation activities[1] are not concerned by this circular and must of course be carried out in the usual way, in accordance with the legal requirements.

2. Legal framework

The national regulatory provisions relating to the RMP's related to medicinal products come under article 6, §1bis, subparagraphs 9 and 10 of the law of 25 March 1964 on medicinal products and under articles 64, §2 and 190 of the royal decree of 14 December 2006 on medicinal products for human and veterinary use.

3. General information

A marketing authorisation (MA) or a registration of a medicinal product can in some circumstances be submitted to certain restrictions or conditions that are formulated within the framework of a RMP.

It can be restrictive conditions concerning:

- the prescription;
- the delivery mode;
- the supplying (e.g. : necessity to implement a restricted or controlled distribution system for a given medicinal product);
- the use or the administration of the medicinal product (e.g. : necessity to supply educational and informative material to the healthcare professionals, patients, veterinarians or animal's owners);
- the carrying out of particular clinical trials.

These conditions, generally gathered together under the term « additional risk minimisation activities » can be imposed:

- or by the European Commission on the basis of an opinion of the European Medicines Agency (EMEA). In concrete terms, these conditions appear in the decision of the European Commission granting marketing authorisation for the medicinal product, in annex II, B, under « conditions or restrictions with regard to the safe and effective use of the medicinal product ». In this case, the European authorities require from the MA holder that he re-examines the details of the required measures or material in agreement with the competent authority of each Member State, that is the FAMHP in Belgium;
- or by the Minister of his delegate in the framework of a MA/registration procedure, a modification of the MA/registration, or a renewal of the MA/registration. The decision is of course taken by taking account of the type of the concerned procedure (mutual recognition, decentralised or national), and so, possibly in consultation with other Member States;
- or by the Minister of his delegate on spontaneous proposal of the MA/registration holder. In this case, the initiative of setting up certain measures or developing particular material comes from the MA/registration holder. This one must then duly justify the measures or the material that he suggests to eliminate or to reduce a given risk.

Whatever the origin of the decision to implement a RMP, any developed material or any other measure that is taken must **absolutely be approved by the Minister or his delegate** before its actual implementation.

The MA or registration holder is responsible for implementing the program within the time limit that is imposed by the competent authorities. Particular attention should be paid to the fact that he must make sure to **take in time** all the necessary steps to my services in order to get the required approval in due time. In this respect, in the particular situation of a program that is imposed by the European Commission on the advice of the CHMP (Committee for Medicinal Products for Human Use) or the CVMP (Committee for Medicinal Products for Veterinary Use) of the EMEA, the national approval procedure that is described hereinafter under point 4 can be started as from the moment the CHMP/CVMP has given a positive opinion in the evaluation process.

I want to point out that the RMP's are in essence developed for the purpose of ensuring as well as possible a safe and effective use of the medicinal product. The content of the various documents that are sometimes required in the programs must inform the target audience in a short, objective and realistic way on the risk in question and on the measures and means that make it possible to reduce or to eliminate it. These documents can under no circumstances convey messages, slogans, logos, pictures or photos of a promotional nature.

4. Approval procedure

The Minister or his delegate approves the various materials or measures that are developed in the framework of the RMP's on the basis of an opinion given by one of the commissions provided under article 122 §1 and article 247 of the royal decree of 14 December 2006 on medicinal products for human and veterinary use, hereinafter called (Medicines) Commission. In agreement with the commissions, the following procedure has been adopted:

a) Submission of the elements to be approved

- The dossier must be submitted by the MA/registration holder to the FAMHP, department Proper Use of Medicines in an electronic device (CD-ROM, USB key, ...) and in paper format (one copy).
- For contact purposes between the FAMHP and the applicant during the evaluation process of the dossier, you are requested to mention the e-mail address of a contact person within the firm.
- Since the evaluation done by the FAMHP concerns the national version of the program, the documents and materials that are required in the program will be submitted in French and/or Dutch. If the program is submitted in only one of these languages, it is requested, following to what is required for the translations of the SPC and the PiL, to send to the FAMHP, after approval, a version in the other language of the approved documents and materials. A version in German of the documents and materials for the patients will also be attached. All these elements will be sent to the FAMHP with a declaration of conformity of the translations.
- When a program concerning a medicinal product for human use provides that documents are intended for healthcare professionals (e.g.: DDL, informative booklet), these documents will contain the following standard sentence: « The Belgian Centre for Pharmacovigilance for medicinal products for human use (CBPH) of the Federal Agency for Medicines and Health Products (FAMHP) reminds the healthcare professionals that it highly recommends, in the framework of its active pharmacovigilance plan, the notification of each serious or suspect adverse reaction to the CBPH. For more information, you can send an e-mail to the CBPH to the following address: adversedrugreactions@afmps.be ».
- When the program contains video material, a copy of this one will be attached to the dossier in a videocassette, DVD or in the form of a detailed storyboard when the video film is not yet available.
- When the program contains varied material (e.g.: medical device for demonstration), a specimen of this material will be attached to the dossier.
- When the program provides that material or documents is/are distributed or made available on a website, it is important to specify in the dossier who is the target audience as well as the means that will be used by the firm to ensure the fact that the documents and the material are effectively distributed and made available for the target audience only.

  These documents and material should be submitted in their final form, already including the possible logos, pictures or photos.

b) Acknowledgement of receipt of the dossier.

  Within fifteen working days following the receipt of the dossier, the department Proper Use of the Medicines of the FAMHP confirms it has been received in proper order by letter and e-mail addressed to the applicant.

c) Request for opinion from the Minister or his delegate to the Commission.

The Commission appoints to that end an expert who examines the submitted dossier and writes his report. This one is then presented and discussed in plenary session of the Commission.

The opinion of the Commission is communicated to the Minister or his delegate.

d) Approval of the program or request for adaptation

- When, on the basis of the opinion given by the Commission, the Minister or his delegate approves the program, he informs the MA/registration holder of it by mail and by e-mail.

- When, on the basis of the opinion given by the Commission, the Minister or his delegate temporarily refuses to approve the program, he informs the MA/registration holder of it by mail and by e-mail and he adds his remarks or objections.
When the firm gives a positive answer to the formulated remarks or objections, the Minister or his delegate approves the program for good and he informs the MA/registration holder of it by mail and by e-mail.
However, when the firm doesn't agree on the formulated remarks or objections, it informs the Minister or his delegate of it. The given arguments are in this case communicated to the Commission, which gives an opinion to the Minister or his delegate (cf. point b). On the basis of this opinion, the Minister or his delegate approves or refuses for good the proposed program and informs the MA/registration holder of it by mail and by e-mail.

I draw your attention to the fact that the later modifications of any approved element will have to be submitted to a prior approval by my services, in accordance with the procedure that is explained hereabove.

5. Particular case of clinical trials

When a measure that is provided in a RMP concerns the execution of a clinical trial, the national approval procedure, mentioned under point 4 hereabove, doesn't apply to this clinical trial. The regulation that applies to clinical trials must on the other hand be respected and serves then as an approval by the Belgian national authority.

I hope we can count on your good cooperation.

Yours faithfully,

Xavier De Cuyper
General Administrator

[1] Cfr Guideline on risk management systems for medicinal products for human use
www.emea.europa.eu/pdfs/human/euleg/9626805en.pdf