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Guideline on good pharmacovigilance practices (GVP)

Module X – Additional monitoring

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X.A. Introduction

Pharmacovigilance is a vital public health function with the aim of rapidly detecting and responding to potential safety hazards associated with the use of medicinal products.

A medicinal product is authorised on the basis that, its benefit-risk balance is considered to be positive at that time for a specified target population within its approved indication (s). However, not all risks can be identified at the time of initial authorisation and some of the risks associated with the use of a medicinal product emerge or are further characterised in the post-authorisation phase of the product's lifecycle. . To strengthen the safety monitoring of medicinal products, the 2010 EU Pharmacovigilance legislation, further amended in 2012, has introduced a framework for enhanced risk proportionate post-authorisation data collection for medicinal products, including the concept of additional monitoring for certain medicinal products.

As defined in Article 23 of Regulation (EC) No 726/2004 (REG) and Article 11 of Directive 2001/83/EC (DIR), the Agency shall, in collaboration with the Member States, set up, maintain and make public a list of medicinal products that are subject to additional monitoring (hereafter referred to as "the list"). These medicinal products will be readily identifiable by an inverted equilateral black triangle ▼ as stipulated in the Implementing Regulation (EU) No 198/2013. That triangle will be followed by an explanatory statement in the summary of product characteristics (SmPC) as follows:

"This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions."

A similar statement will also be included in the package leaflet. This explanatory statement should encourage healthcare professionals and patients to report all suspected adverse reactions.

The pharmacovigilance provisions of Regulation (EC) No 726/2004 and of Directive 2001/83/EC have been recently amended by Regulation (EU) No 1027/2012 and Directive 2012/26/EU respectively. These amendments have impacted on the content and the scope of Article 23 of the REG and will be applicable for centrally authorised products on 5 June 2013. This GVP takes into account the new provisions relating to the list of products which require additional monitoring.

Post-authorisation spontaneous Adverse Drug Reactions (ADR) reports remain a cornerstone of pharmacovigilance. Data from ADR reports is a key source of information for signal detection activities (see [Module IX](#)). Increasing the awareness of healthcare professionals and patients of the need to report suspected adverse drug reactions and encouraging their reporting is therefore an important means of monitoring the safety profile of a medicinal product.

The concept of additional monitoring originates primarily from the need to enhance the ADR reporting rates for newly authorised products for which the safety profile might not be fully characterised or for products with newly emerging safety concerns that also need to be better characterised. The main goals are to collect additional information as early as possible to further elucidate the risk profile of products when used in clinical practice and thereby informing the safe and effective use of medicinal products.

This Module is divided in two sections:

- [X.B.](#) provides general principles for assigning additional monitoring status to medicinal products and on communication and transparency aspects.
- [X.C.](#) describes the operation of the EU network regarding the supervision of additional monitoring status, the communication strategy and the impact on pharmacovigilance activities.

X.B. Structures and processes

X.B.1. Principles for assigning additional monitoring status to a medicinal product

All medicines are authorised on the basis that the benefit of treatment is considered to outweigh the potential risks. To come to this conclusion for a marketing authorisation, data from clinical trials conducted during the development of a medicine are assessed. However, adverse reactions which occur rarely or after a long time may become apparent only once the product is used in a wider population and/or after long term use. In addition, the benefits and risks of a medicine may have been evaluated in conditions which may differ from those in everyday medical practice, e.g. clinical trials might exclude certain types of patients with multiple co-morbidities or concomitant medications. Therefore, after a medicine is placed on the market, its use in the wider population requires continuous monitoring. Marketing authorisation holders and competent authorities continuously monitor medicinal products for any information that becomes available and assess whether it impacts on the benefit-risk profile of the medicinal product. However, for certain medicinal products enhanced post-authorisation data collection is needed to ensure that any new safety hazards are identified as promptly as possible and that appropriate action can be initiated immediately. Therefore, in order to strengthen the monitoring of certain medicinal products and in particular to encourage the spontaneous reporting of ADRs, the concept of additional monitoring has been introduced.

Additional monitoring status can be assigned to a medicinal product at the time of granting a marketing authorisation or in some cases at later stages of the product life cycle for a medicinal product for which a new safety concern has been identified. The additional monitoring status is particularly important when granting marketing authorisation for medicinal products containing a new active substance and for all biological medicinal products, which are priorities for pharmacovigilance. Competent authorities may also require additional monitoring status for a medicinal product which is subject to specific obligations e.g. the conduct of a Post-Authorisation Safety Study (PASS) or restrictions with regards to the safe and effective use of the medicinal product.

X.B.2. Communication and transparency

The additional monitoring status needs to be communicated to healthcare professionals and patients in such a way that it increases reporting of suspected adverse reactions without creating undue alarm. This can be achieved for example by highlighting the need to better characterise the safety profile of a new medicinal product by identifying additional risks but placing those potential risks in the context of the known benefits for this product. A publicly available list of medicinal products with additional monitoring status should be kept up to date by the Agency. In addition, healthcare professionals and patients should be enabled to easily identify those products through their product labelling. The publication of the list together with appropriate communication should encourage healthcare professionals and patients to report all suspected adverse drug reactions for all medicinal products subject to additional monitoring.

X.C. Operation of the EU network

X.C.1. Criteria for including a medicinal product in the additional monitoring list

X.C.1.1. Mandatory scope

According to Article 23(1) of Regulation (EC) No 726/2004 (REG), it is mandatory to include the following categories of medicinal products in the list:

- medicinal products authorised in the EU that contain a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- any biological medicinal product not covered by the previous category and authorised after 1 January 2011;
- products for which a PASS was requested at the time of marketing authorisation (point (cb) of Article 9(4) of Regulation (EC) No 726/2004 and point (b) of Article 21a of Directive 2001/83/EC);
- products authorised with specific obligations on the recording or suspected adverse drug reactions exceeding those referred to in Chapter 3 of Directive 83/2001/EC (point (cb) of Article 9(4) of Regulation (EC) No 726/2004 and point (c) of Article 21a of Directive 2001/83/EC);
- products for which a PASS was requested following the grant of marketing authorisation (Article 10a(1) of Regulation (EC) No 726/2004 and point (a) of Article 22a (1) of Directive 2001/83/EC);
- products which were granted a conditional marketing authorisation (Article 14(7) of Regulation (EC) No 726/2004);
- products authorised under exceptional circumstances (Article 14(8) of Regulation (EC) No 726/2004 and Article 22 of Directive 2001/83/EC).

X.C.1.2. Optional scope

As set out in Article 23(2) of Regulation (EC) No 726/2004 there is the possibility to include in the list medicinal products subject to conditions, not falling under the mandatory scope. This can be done at the request of the European Commission or a national competent authority, as appropriate, following consultation with the Pharmacovigilance Risk Assessment Committee (PRAC).

As reflected in Article 23(2) of Regulation (EC) No 726/2004 the situations that could form the basis for a request for inclusion in the list are:

- When a marketing authorisation is granted subject to one or more of the following:
 - conditions or restrictions with regard to the safe and effective use of the medicinal product [REG Art 9(4)(c), DIR Art 21a(d)];
 - measures for ensuring the safe use of the medicinal product to be included in the risk management system [REG Art 9(4)(ca), DIR Art 21a(a)];
 - an obligation to conduct a post-authorisation efficacy study [REG Art 9(4)(cc)DIR Art 21a(f)];
 - the existence of an adequate pharmacovigilance system [DIR Art 21a(e)].

The scope of Article 23(2) of Regulation (EC) No 726/2004 does not only include medicinal products which are authorised or for which conditions are established after entry into force of the new pharmacovigilance legislation but also medicinal products which were authorised or made subject to

conditions before such date, provided they fall within one or more of the above situations for the optional scope.

Pharmacovigilance rules in general and additional monitoring specifically take into account that the full safety profile of medicinal products can only be confirmed after products have been placed on the market. Due consideration should, therefore, be given to the merit of inclusion of a medicinal product in the list in terms of increasing awareness about the safe and effective use of a medicinal product and/or providing any additional information for the evaluation of the product. In this regard, the decision to include a medicinal product subject to conditions in the list should take account of the nature and scope of the conditions or obligations placed on the marketing authorisation including their potential public health impact. The decision should also consider the usefulness of the additional monitoring status in relation to other additional pharmacovigilance activities proposed in the risk management plan, for example in relation to the objectives of PASS.

X.C.2. Criteria for defining the initial time period of maintenance in the additional monitoring list

X.C.2.1. Mandatory scope

For medicinal products containing new active substances as well as for all biological medicinal products approved after 1 January 2011 the initial period of time for inclusion is five years after the Union Reference Date (URD) referred to in Article 107c(5) of Directive 2001/83/EC.

X.C.2.2. Optional scope

The period of time for inclusion in the list of medicinal products authorised subject to conditions is decided by the European Commission or the national competent authority, as appropriate, is linked to the fulfilment of the conditions and obligations placed on the marketing authorisation.

If new conditions are imposed to the marketing authorisation during a product's lifecycle, it is envisaged that a medicinal product previously removed from the list can be added to the list again if for example the criteria stipulated in Article 23(2) of Regulation (EC) No 726/2004 are met again.

X.C.3. Roles and responsibilities

X.C.3.1. The European Commission

The European Commission decides, based on a recommendation from the PRAC:

- if a particular centrally authorised medicinal product subject to conditions as set out in Article 23(2) of Regulation (EC) 726/2004 should be included in the list.

X.C.3.2. The Agency

The Agency:

- is responsible for publishing the list of medicinal products that are subject to additional monitoring on the European web-portal with an electronic link(s) to a webpage where the product information and the summary of the RMP are publicly available;
- will coordinate the gathering of information that should be sent by the competent authorities within the EU network in order to set up, maintain and publish the list;
- is responsible for removing medicinal products from the list after a pre-determined time period;

- will take into account the list of centralised medicinal products subject to additional monitoring in determining the frequency and processes of its signal detection activities;
- will inform the relevant MAH when a centralised medicinal product has been included to the list of additional monitored products;
- will support the process of consultation of the PRAC on the inclusion of medicinal products on the list.

X.C.3.3. National competent authorities

National competent authorities should:

- inform the Agency which nationally authorised medicinal products are to be included in the list and provide the electronic links to the national webpage where the product information and the summary of the RMP are publicly available;
- decide, based on a recommendation from the PRAC, if a particular nationally authorised medicinal product subject to conditions as set out in Article 23(2) of Regulation (EC) 726/2004 should be subject to additional monitoring and therefore included in the list;
- make publicly available in their national web-portal the list of medicinal products authorised in their territory that are subject to additional monitoring. The list shall include an electronic link to a webpage where the product information and the summary of the RMP are publicly available;
- inform the Agency of any update that needs to be made for nationally authorised medicinal products included in the list that is published by the Agency;
- take into account the list of nationally authorised medicinal products subject to additional monitoring in determining the frequency and processes of their signal detection activities;
- inform the relevant MAH when a nationally medicinal product has been included to the list of additional monitored products.

X.C.3.4. The Pharmacovigilance Risk Assessment Committee (PRAC)

The PRAC:

- recommends, upon request of the European Commission or a national competent authority, as appropriate, if a medicinal product which is subject to conditions as set out in Article 23(2) of Regulation (EC) 726/2004 should be included in the list.

X.C.3.5. The Marketing authorisation holder

The marketing authorisation holder:

- shall include in the SmPC and Package leaflet of their medicinal products subject to additional monitoring the black triangle symbol ▼ and the and the standardised explanatory statement on additional monitoring;
- should include information on the status of additional monitoring in any material to be distributed to healthcare professionals and patients and should make all efforts to encourage reporting of adverse reactions, as agreed with national competent authorities;
- should provide evidence to the competent authorities concerned on the status of any conditions imposed by the national competent authorities or the European Commission;

- should submit the relevant variation to include/remove the black symbol, the statement, and the standardised explanatory sentence from the SmPC and PL, where applicable.

X.C.4. Creation and maintenance of the list

As defined in Article 23 of Regulation (EC) 726/2004 the Agency shall, in collaboration with the Member States, set up, maintain and make public a list of medicinal products that are subject to additional monitoring. This list will include the names and active substances of all medicinal products approved in the EU subject to additional monitoring irrespective of the approval procedure (i.e. centrally or nationally authorised). In addition, as defined in Article 106 of Directive 2001/83/EC, each Member State shall make publicly available on their national web-portal the list of medicinal product authorised in their territory that are subject to additional monitoring, and take all appropriated measures to encourage patients and health care professional to report any suspected adverse drug reactions.

X.C.4.1. Process for the creation of the list

The Agency in support of the European Commission will identify the centrally authorised products requiring additional monitoring. National competent authorities are responsible for identifying the nationally authorised products requiring additional monitoring.

Only medicinal products that fall under the mandatory scope according to Article 23(1) of Regulation (EC) 726/2004 will be automatically included in the list. For medicinal products that fall under the optional scope, consultation with the PRAC is required.

The Agency and the national competent authorities will maintain the information that is publicly available and ensure that it is up to date. While the Agency will have direct access to relevant data for centrally authorised products, for nationally authorised products, the Agency will rely on accurate and timely information provided by national competent authorities with regard to the inclusion or removal of medicinal products from the list and the provision of the electronic links to the national web-portals where the product information and the summary of the RMP are publicly available.

The Agency and the Members States will make the list available to the public.

X.C.4.2. Process for the maintenance of the list

The list will be updated monthly following each PRAC meeting, as appropriate.

X.C.4.2.1. Inclusion of medicinal products in the list

Mandatory scope

According to Article 23(1) of Regulation (EC) 726/2004 medicinal product that fall under the mandatory scope will be automatically included in the list on an ongoing basis. In case of medicinal products approved through the mutual recognition or decentralised procedures, the Reference Member State (RMS) should inform the Agency once authorisation for such products has been granted. In addition, each national competent authority included in such procedures should inform the Agency, within 15 days of granting the marketing authorisation nationally, and provide the electronic links to their national web-portal where the product information and the summary of the RMP are publicly available. The Agency will include medicinal products in the list within the next update following receipt of the European Commission decision, in case of centrally authorised products, or following receipt of the national competent authorities' notification.

Optional scope

According to Article 23(2) of Regulation (EC) No 726/2004 medicinal products that fall under the optional scope, consultation with the PRAC is required prior to inclusion in the list.

In case of mutual recognition or decentralised procedures, the RMS should be the lead and consult the PRAC as soon as relevant conditions are considered necessary and before the finalisation of the procedure.

In case of purely national procedures, the national competent authority should consult the PRAC as soon as relevant conditions are considered necessary and before the finalisation of the procedure.

The Agency will include centrally authorised products in the list within 15 days of receipt of the European Commission decision. For non-centrally authorised products, once a procedure is finalised each national competent authority should inform the Agency within 15 days on those particular medicinal products that are to be included in the list and provide the electronic links to their national web-portal where the product information and the summary of the RMP are publicly available.

X.C.5. Black symbol and explanatory statements

For medicinal products included in the list, the SmPC shall include the statement:

“This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.”,

preceded by an inverted equilateral black triangle (Implementing Regulation (EU) No 198/2013). A similar statement will also be included in the package leaflet. Once the medicinal product is included or removed from the list, the marketing authorisation holder shall update the SmPC and the package leaflet to include or remove, as appropriate, the black symbol, the statement, and the standardised explanatory statement.

If the decision to include or remove a medicinal product from the list is done during the assessment of a regulatory procedure (e.g. marketing authorisation application, extension of indication, renewal) the SmPC and the package leaflet should be updated before finalisation of the procedure in order to include or remove the black triangle symbol and explanatory statement from the product information.

If the decision to include or remove a medicinal product from the list is done outside a regulatory procedure, then the marketing authorisation holder is requested to subsequently submit a variation to update the product information of that product accordingly.

X.C.6. Transparency

Pursuant to Article 23 of Regulation 726/2004, the Agency will make publicly available the list of the names and active substances of all medicinal products approved in the EU subject to additional monitoring and the general criteria to include medicinal products in the list. The national competent authority shall also make publicly available the list of medicinal products authorised in their territory that are subject to additional monitoring.

The list will include an electronic link(s) to the relevant web-portal where the product information and the summary of the RMP are publicly available.