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# 3 Guideline on good pharmacovigilance practices (GVP)

## 4 Module X – Additional monitoring

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| Comments should be provided using this template. The completed comments form should be sent to gvp@ema.europa.eu |

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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 in the specified indication(s), at the time of authorisation, the risk-benefit balance is judged to be positive for the target population. However, not all risks can be identified at the time when an initial authorisation is sought and many of the risks associated with the use of a medicinal product can only be discovered or fully characterised post-authorisation. To strengthen the safety monitoring of medicinal products, the 2010 EU Pharmacovigilance legislation has introduced a framework for enhanced risk proportionate post-authorisation data collection for medicinal products, one element of which is the concept of additional monitoring for certain medicinal products.

As defined in Article 23 of Regulation (EC) No 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 (hereafter referred to as "the list"). These medicinal products will be readily identifiable by the introduction of the statement "This medicinal product is subject to additional monitoring" preceded by a standard black symbol and followed by an appropriate standardised explanatory statement in their summary of product characteristics (SmPC) and package leaflets (PL). This explanatory statement should encourage healthcare professionals and patients to report all suspected adverse reactions.

Post-authorisation spontaneous adverse reaction reports remain a cornerstone of pharmacovigilance. Data from spontaneous suspected adverse drug reactions (ADR) 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 reactions and encouraging their reporting is therefore a potentially important means of monitoring the safe use of a medicinal product.

The concept of additional monitoring originates primarily from the need to increase the proportionality between ADR reporting and the level of knowledge about the safety of a product and to allow a differentiated view of specific medicines. 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 to increase awareness about the safe and effective use of certain medicinal products. It is important to emphasize, however, that this concept does not lead to earlier granting of a marketing authorisation. This Module is divided in two sections:

- section X.B. provides general principles for assigning additional monitoring status to medicinal products and on the communication and transparency aspects.
- section 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. General principles for assigning additional monitoring status to a medicinal product*

All medicines are authorised on the basis that the benefit of treatment is judged to outweigh the potential harm. 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 used in

everyday medical practice where patients may have more than one disease or treatment is frequently not studied before authorisation. Therefore, after a medicine is placed on the market, its use in the wider population requires continuous monitoring. As for all medicinal products, marketing authorisation holders and competent authorities continuously monitor any information that becomes available and assess the impact on the risk-benefit 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 new EU Pharmacovigilance legislation has introduced the concept of additional monitoring.

Additional monitoring status can be assigned to a medicinal product at the time of granting marketing authorisation or at any time of the product life cycle. 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. to conduct a post-authorisation safety study or to conditions or restrictions with regard 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 but without creating undue alarm. A publicly available list of medicinal products with additional monitoring status should be kept up to date by the competent authorities. 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 reactions while supervising or receiving treatment with a medicinal product subject to additional monitoring.

## *X.B.3. Quality systems and record management*

An essential feature of the process for the creation and maintenance of the list and for the communication of the status of additional monitoring is that it is clearly documented to ensure that the system functions properly and effectively, that the roles, responsibilities and required tasks are conducted in a timely manner and are clear to all parties involved. Therefore, a system of quality assurance and quality control consistent with the quality system standards should be in place and applied to processes (see Module I).

Detailed procedures for this quality system should be devised, documented and implemented. The organisational roles and responsibilities for the activities and maintenance of documentation, quality control and review, and for ensuring corrective and preventive action should be assigned and recorded.

# 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, it is mandatory to include the following two categories of medicinal products in the list:

1. 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;
2. any biological medicinal product not covered by the previous category and authorised after 1 January 2011.

### X.C.1.2. Optional scope

As set out in Article 23(2) of Regulation (EC) No 726/2004 there is also 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 the 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)];
  - to take certain 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)];
  - to conduct post-authorisation safety studies (PASS) [REG Art 9(4)(cb), DIR Art 21a(b)];
  - to comply with obligations on the recording or reporting of suspected adverse reactions which are stricter than those referred to in Chapter 3 of Regulation (EC) No 726/2004 or in Title IX of Directive 2001/83/EC [REG Art 9(4)(cb), DIR Art 21a(c)];
  - to conduct a post-authorisation efficacy study [REG Art 9(4)(cc), DIR Art 21a(f)];
  - conditional approval, i.e. authorisation is granted subject to certain specific obligations (e.g. the performance of further studies), to be reviewed annually by the Agency [REG Art 14(7)];
  - marketing authorisation under exceptional circumstances [REG Art 14(8), DIR Art 22];
  - the existence of an adequate pharmacovigilance system [DIR Art 21a(e)].
- When a competent authority imposes one or both of the following obligations on the marketing authorisation holder after the granting of a marketing authorisation [REG Art 10(a), DIR Art 22a]:
  - to conduct a post-authorisation safety study (PASS);
  - to conduct a post-authorisation efficacy study (PAES).

- When a competent authority imposes an obligation on a marketing authorisation holder to operate a risk management system for a medicinal product approved before 2 July 2012 [REG Art 21(2)] or 21 July 2012 [DIR Art 104a].

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 described situations.

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 post-authorisation safety studies (PASS).

If a reference medicinal product that is subject to conditions is included in the list, due consideration should be given to include any generics of this reference medicinal product in the list taking into account that the conditions or obligations imposed on the marketing authorisation for a generic may be different to the ones of the reference medicinal product.

## *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 referred to in Article 107c(5) of Directive 2001/83/EC .

### X.C.2.2. Optional scope

The initial period of time for inclusion in the list of medicinal products authorised subject to conditions can be decided by the European Commission or the national competent authority, as appropriate, following recommendation from the PRAC, taking account of the time considered necessary to fulfil the conditions and obligations placed on the marketing authorisation.

## *X.C.3. Criteria for revision: extension of the period or deletion from the list*

Once a medicinal product is included in the list for a certain period of time the European Commission or the national competent authority, as appropriate, may extend that period following the recommendations of the PRAC and taking into account the time considered necessary to conclude that the conditions referred to in Articles 14a and 21(2) of Regulation (EC) 726/2004 or referred to in Articles 22b and 104a of Directive 2001/83/EC have been fulfilled.

### X.C.3.1. Mandatory scope

In the case where a medicinal product is automatically included in the list at the time of granting of the marketing authorisation, consideration of removal from the list at the five year time point will normally be linked with the renewal procedure. In cases where the removal of a medicinal product from the list cannot be linked with the renewal procedure (e.g. informed consent or duplicate applications), the product will be removed from the list by default 5 years after the URD, unless a different decision has been taken during the renewal of the first medicinal product authorised in EU containing the same active substance. During the renewal, the European Commission or the national competent authority, as appropriate, should indicate if the medicinal product should be maintained in the list if justified 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. The criteria for extending the period of inclusion should take into account the frequency of submission of PSURs and the need for an additional renewal. In order to determine the length of the extension, the period of time needed for completion of milestones in the RMP should be taken into account.

### X.C.3.2. Optional scope

In case a medicinal product is added to the list for an initial defined period of time following a recommendation from the PRAC, consideration of removal of the medicinal product from the list will depend on the fulfilment of the conditions placed on the marketing authorisation and on the knowledge of the safety profile gathered by that time.

As part of the evaluation of the data submitted by the marketing authorisation holder (i.e. renewal procedure, PSURs, study reports, RMP updates) the European Commission or the national competent authority, as appropriate, following a recommendation of the PRAC, may propose to extend that period of additional monitoring for the time considered necessary.

If there is no recommendation to extend the time period of additional monitoring of the reference medicinal product, removal from the list should apply to all generic medicinal products, unless different conditions and milestones have been agreed.

If new conditions are imposed after the granting of the marketing authorisation, it is envisaged that a medicinal product previously removed from the list can be added again or, if the medicinal product is already in the list, the initial fixed time period of inclusion can be extended.

## *X.C.4. Roles and responsibilities of the key stakeholders*

### X.C.4.1. 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;
- the time period for which a particular centrally authorised medicinal product subject to conditions as set out in Article 23(2) of Regulation (EC) 726/2004 should remain in the list;
- whether the period of additional monitoring for a centrally authorised product is extended beyond the initial agreed period.

### X.C.4.2. 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, unless the European Commission or the national competent authority, based on a recommendation from the PRAC, decide that the period of additional monitoring should be extended.

### X.C.4.3. National competent authorities

National competent authorities:

- inform the Agency on those particular nationally authorised medicinal products that 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;
- decide, based on a recommendation from the PRAC, the time period that a particular nationally authorised medicinal product subject to conditions as set out in Article 23(2) of Regulation (EC) 726/2004 is to remain in the list;
- decide, based on a recommendation from the PRAC, whether the period of additional monitoring for a nationally authorised medicinal product is to be extended beyond the initial fixed time period;
- shall 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.

### X.C.4.4. The Pharmacovigilance Risk Assessment Committee (PRAC)

The Pharmacovigilance Risk Assessment Committee (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;
- recommends upon request of the European Commission or a national competent authority, as appropriate, the necessity of the extension of the additional monitoring period beyond the initial time period:

### X.C.4.5. Marketing authorisation holders

Marketing authorisation holders:

- shall include in the SmPC and PL of their medicinal products subject to additional monitoring the black symbol, the statement “This medicinal product is subject to additional monitoring”, and the standardised explanatory sentence;

- 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;
- shall provide evidence on the status of any conditions imposed by the national competent authorities or the European Commission;
- shall 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.5. 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.

### X.C.5.1. Process for the creation of the list

The Agency is responsible for identifying 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.5.2. Process for the maintenance of the list

The list will be updated monthly following each PRAC meeting, if required.

#### *X.C.5.2.1 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 product approved through the mutual recognition or decentralised procedures, the Reference Member State (RMS) should inform the Agency once the procedure is finalised. In addition, each national competent authority shall inform the Agency, within 15 days of granting the marketing authorisation, 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. 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 centralised procedure, the Committee for Medicinal Products for Human Use (CHMP) should consult the PRAC as soon as conditions are considered necessary and before the finalisation of the procedure.

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

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

A PRAC recommendation is sent to the CHMP, RMS, or national competent authority, as applicable. In the case where the CHMP or national competent authority (ies), as applicable, does not follow the PRAC recommendation a justification should be provided in the public assessment report. The final decision should be communicated to the Agency once the procedure is finalised. The final decision shall be implemented in all concerned member states.

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.5.2.2 Extension of the period of time or deletion from the list*

Unless the European Commission or the national competent authority, as applicable, has informed the Agency that the period of maintenance in the list is extended, the Agency will consult the CHMP, the reference member state or the national competent authority, as appropriate before removing medicinal products from the list at the end of the pre-determined time period. In order to extend the period of maintenance in the list, PRAC must be consulted.

A PRAC recommendation is sent to the CHMP, RMS, or national competent authority, as applicable. In the case where the CHMP or national competent authority (ies), as applicable, does not follow the PRAC recommendation a justification should be provided in the public assessment report. The final decision should be communicated to the Agency within 15 days and implemented in all concerned member states.

#### *X.C.5.2.3 Communication tool*

The European pharmacovigilance issues tracking tool should be used to provide the information needed to set up and maintain the list, such as, the name of the medicinal product, the active substance(s), the Union Reference Date, the proposed date of removal/proposed extended period and the electronic link(s) to the national web-portal where the product information and the summary of the RMP are publicly available.

## X.C.6. Black symbol and explanatory statements

For medicinal products included in the list, the SmPC and the package leaflet shall include the statement “This medicinal product is subject to additional monitoring”. This statement shall be preceded by a black symbol, which is selected by the European Commission on the basis of a recommendation by the PRAC and followed by an explanatory sentence explaining the concept of additional monitoring.

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, as appropriate, the statement, the black 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 the relevant variation to include or remove, as appropriate, the black symbol, the statement, and the standardised explanatory statement.

## X.C.7. Transparency

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 to the summary of the RMP are publicly available.

## X.C.8. Impact on the overall pharmacovigilance activities

The publication of the Union list of medicinal products subject to additional monitoring together with the statement, the black symbol and the standardised explanatory sentence included in the SmPC and the package leaflet of these medicinal products increases transparency and enhances the communication to healthcare professionals and patients to report suspected adverse reactions. The main goal is to facilitate the ready identification of medicinal products that require collection of additional information in a timely manner. As for all medicinal products, marketing authorisation holders and competent authorities should continuously monitor any information that becomes available and assess the impact on the risk-benefit profile of the medicinal product. However, in the light of the direct relevance of spontaneous adverse reaction reporting to signal detection activities, the frequency for reviewing the statistical outputs from EudraVigilance for competent authorities should be every 2 weeks for the duration of the additional monitoring (see Module IX).