EUROPEAN MEDICINES AGENCY
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# List of European Union reference dates and frequency of submission of Periodic Safety Update Reports

Introductory cover note to the public consultation of the EU reference dates list

## 1. Introduction

The list of Union reference dates and frequency of submission of periodic safety update reports (referred to as the "EU reference dates list" in the Good Vigilance Practice Module VII on Periodic Safety Update Reports) consists of a comprehensive list of active substances and combinations of active substances sorted in alphabetical order, for which Periodic Safety Update Reports (PSURs) shall be submitted in accordance with the EU reference dates and frequencies determined by the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) following consultation with the Pharmacovigilance and Risk Assessment Committee (PRAC) [DIR Art. 107c(4) and (6)*].

The EU reference dates list has been built in order to facilitate the harmonisation of Data Lock Points (DLPs) and frequency of submission of PSURs for medicinal products containing the same active substance or the same combination of active substances subject to different marketing authorisations, authorised in more than one Member State. This will, where appropriate, allow the single assessment of the related PSURs as set out in [DIR Art. 107e].

The list is intended to optimise the management of PSURs assessment within the EU while supporting transparency, and to provide predictability to the various stakeholders in terms of workload related to PSURs taking into account the currently known safety profile of the active substances and combinations of active substances. The EU Regulatory Network considers the list as the relevant tool to anticipate as much as possible the PSUR-related activities while bearing in mind that competent authorities in Member States can request the submission of PSURs at any time [DIR Art. 107c (2)]. The list will be "live", i.e. that it can be amended whenever considered necessary by the PRAC, CHMP or CMDh.

* Guidelines on good pharmacovigilance practices (GVP) - Introductory cover note to the public consultation of the first seven modules: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf *"In GVP, any reference to Regulation (EC) No 726/2004 and Directive 2001/83/EC refers to the Regulation and Directive respectively, always including their latest amendments. Where reference is made to specific Articles in square brackets "REG" means Regulation (EC) No 726/2004 as amended and "DIR" means Directive 2001/83/EC as amended."*

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The EU Regulatory Network decided to seek input from stakeholders by mean of this public consultation in order to facilitate the finalisation of the EU reference dates list to be adopted by the CHMP and CMDh following consultation of the PRAC.

This consultation will help reduce the number of future requests for changes related to the PSUR frequency and submission dates.

For more details on how the list will support the coordination of PSUR-related activities, please see sections 4 (Public Consultation), 5 (Timelines) and 6 (Instructions for providing comments) of this document.

# 2. Scope of the EU reference dates list

A detailed description of the EU reference dates list is included in the Guideline on good pharmacovigilance practices (GVP), Module VII – Periodic safety update report (VII.C.3), which is currently under public consultation.

The PSUR frequency as published on the EU reference dates list for a given active substance or combination of active substances overrules the submission schedule described in [DIR Art 107c (2)] and any conditions related to the frequency of submission of PSURs included in the Marketing Authorisation.

As a result of the publication of the EU reference dates list, any changes to the PSUR submission frequency and dates of submission / DLP will trigger the obligation of the MAHs to submit a variation for the products where contradictory requirements are specified in the Marketing Authorisation [DIR 107c(4) and (6)].

*Note: The EU reference dates list will replace the current PSUR Work sharing and Synchronisation lists.*

The following special considerations are highlighted in the EU reference dates list when relevant:

- If different PSURs should be submitted for medicinal products containing the same active substance and authorised for one MAH depending on different indications, routes of administration, dosage forms and dosing regiments [IM Annex III. 1 (7)[†]]. In the case where different PSURs are required, the active substance or combination of active substances appears several times in the list including in brackets the scope that should be covered by the PSUR (e.g. PSUR for "topical formulations" versus PSUR for "oral formulation");
- If a stand-alone PSUR should be submitted for fixed dose combination products [IM Annex III. 1 (8)];
- If PSURs for generics, well-established use, traditional herbal and homeopathic medicinal products have been requested by a competent authority in a Member State on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs relating to an active substance [DIR 107b (3) (b)].

[†] Guidelines on good pharmacovigilance practices (GVP) - Introductory cover note to the public consultation of the first seven modules: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf "*Reference to specific Articles of the draft Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC is provided in square brackets with the indication "IM*".

# 3. Development of the list

The draft EU reference dates list was developed using the following data sources: the Eudravigilance Medicinal Product Dictionary (EVMPD), the PSUR Work Sharing (WS) and Synchronisation lists.

The competent authorities in the Member States have been consulted over the last 6 months in the preparation of the list in order to identify the European Union Reference Dates, DLPs and PSUR submission frequencies based on the risk-benefit profile as currently known for each active substance and combination of active substances (reference to GVP VII.C.3.4).

It is important to underline that given the objectives of the EU reference dates list (see section **1. Introduction**) and a risk-based approach adopted by the EU Regulatory Network to propose the PSUR submission frequencies and DLPs, the EU reference dates list can deviate from the PSUR submission schedule defined in [DIR Art 107c(2)(b)].

In parallel and while taking into account the derogation laid down in Article [DIR Art 107b (3)], the Committee on Herbal Medicinal Products (HMPC) was requested to identify in consultation with Member States the herbal substances, herbal preparations, combinations of herbal substances and herbal preparations, homeopathic medicinal products and traditional herbal medicinal for which a reassessment of the safety profile through a single assessment of PSURs is needed. These specific items have been included in the draft EU reference dates list together with a PSUR frequency and DLP.

# 4. Public consultation

## *4.1. Structure of the draft EU reference dates list published for consultation*

The current draft EU reference dates list contains 3155 active substances and combination of active substances. It will be adopted after July 2012 by the CHMP and CMDh following consultation of the PRAC. The content of each column is described in the following table:

| Column Name | Column Description | Any additional information |
|---|---|---|
| **ID Codes** | An ID code is assigned to each active substance and combination of active substances in the list in order to facilitate data quality management. | Any comments made on the draft EU reference dates list should indicate the ID of the active substance or combination of active substances. |
| **Names of active substances or combination of active substances** | The names of the active substances and the combination of active substances are in English.<br>The names indicated in the list correspond to the terms as included in the EVMPD and former Work Sharing and Synchronisation lists. | Any comments made on the draft EU reference dates list should indicate the name of the active substance or combination of active substances. |

| Column Name | Column Description | Any additional information |
|---|---|---|
| **European Union reference dates** | Date of the first or the earliest known date of the marketing authorisation in the Union of a medicinal product containing the active substance or combination of active substances | [DIR Art 107c (5) (a,b)] |
| **PSUR Frequency** | PSUR frequencies as determined by the EU Regulatory Network on the basis of the EU reference date and current Risk-Benefit profile of the active substances or combination of active substances. | The substances or combination of active substances marked with the PSUR frequencies "**> 5 years**" or "**> 10 years**" will have their frequency determined at a later stage.[‡] |
| **Data Lock Point** | The Data Lock Point as determined by the EU Regulatory Network on the basis of the EU reference date and the PSUR submission frequency of the active substances or combinations of active substances. | The substances or combination of active substances marked with DLPs "**01/01/2025***" or "**01/01/2030***" will have their DLP determined at a later stage (see footnote for column "**PSUR Frequency**"). They correspond to the entries identified with the PSUR frequencies "**> 5 years**" or "**> 10 years**". |
| **Are PSURs required for Generic medicinal products?** | Column indicating whether PSURs for Generic Medicinal products should be submitted to be part of a PSUR single assessment. | [DIR Art 107b(3)]<br>No PSUR required for Generic medicinal products except for those where a condition providing for PSUR submission is included in the Marketing Authorisation, or when specified in the list following consideration by a Competent Authority in a Member State (on the basis of pharmacovigilance concern or due to a lack of PSURs for a given active substance).<br>Refer to: GVP Module VII, Section VII.C.3.3.2 |

## *4.2. Scope of the Public Consultation*

Stakeholders, in particular MAHs of the originator medicinal products[§] containing an active substance or a combination of active substances included in the draft EU reference dates list are invited to identify any compelling need for changes on the grounds specified in [DIR Art 107c(6)]:

[‡] However no PSUR submission is required in the period up to 5 or 10 years, unless the frequency is subsequently modified upon request of the PRAC, CHMP or CMDh or specifically required by National Competent Authorities/EMA.
[§] MAHs of the originator products will likely take responsibility in the future for entry of structured substance information in the XEVMPD (X Eudravigilance Medicinal Products Dictionary)

*"The marketing authorisation holders shall be allowed to submit request to the CHMP or the CMDh, as appropriate, to determine the Union reference dates or to change the frequency of submission of PSUR on one of the following grounds:*

- *for reasons relating to public health;*
- *in order to avoid a duplication of the assessment;*
- *in order to achieve international harmonisation."*

In addition to submitting comments with relevance to the above legal provisions, MAHs are requested to indicate whenever a date is currently missing in column C of the draft list, the date of the **first marketing authorisation in the Union or alternatively the International Birth Date of their originator medicinal products containing the active substances and combinations of active substances.**

# 5. Timelines

The public consultation is open from the **4th of April 2012 to the 4th of June 2012.**

After this deadline, the requests/comments will be compiled and tracked before being analysed by the EU Regulatory Network. Changes to the EU reference dates list will be applied to the active substances and combinations of active substances when considered appropriate.

The updated EU reference dates list will thereafter be provided to the PRAC for review, prior to adoption by the PRAC, CHMP and CMDh and formal publication for entry into force.

# 6. Instructions for providing comments

In order to be considered, any comments to the draft EU reference dates list should be included in the pre-formatted excel table available from the link:

http://www.ema.europa.eu/ema/index.jsp?curl=/pages/news_and_events/news/2012/03/news_detail_001479.sjsp&jsenabled=true

Stakeholders should complete the fields "Administrative Information" to ensure all requests/comments are correctly tracked.

The format of the table and the relevant instructions are as follows:

| Category of Request/Comment | Request for change | Details on justification | MAH of the originator product |
|---|---|---|---|
| *Select the relevant category from the drop down list of options based on DIR Art 107c (6)* | *Clearly define here your request* | *Provide details to justify your request.* | *Confirm that you are the MAH of the originator product* |

To comment, the requester should complete the cells as presented above corresponding to a specific active substance or combination of active substances:

- Select the relevant category of request/comment using the available drop down list that appears when clicking on the cells of the column "Category of Request/Comment",
- In case of more than two comments related to the same active substance or combinations of active substances, select in the Column "Category of Request/Comment" the option "Other/ Multiple Comments".
- Provide only one copy of the file including all the requests/comments listed one after another.

The completed excel files should be sent to the following email address: EURDList@ema.europa.eu

To propose a new active substance or combination of active substances to be included to the EU reference dates list provided it enters under the scope described in this document, please clearly indicate the following information in the cover note of the email submitted to the EURDList mailbox:

- Name of the active substance or combination of active substances,
- URD,
- Current marketing authorisation status and Countries where the originator product is authorised,
- Name of the MAH of the originator product,
- Justification for inclusion in the list.

These requests will then be compiled and analysed by the EU Regulatory Network.