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Introductory cover note to the List of European Union reference dates and frequency of submission of Periodic Safety Update Reports

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1. Introduction

The list of Union reference dates and frequency of submission of periodic safety update reports (referred to as the "EU reference dates (EURD) list" in the GVP Module VII) consists of a 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 Risk Assessment Committee (PRAC) [DIR Art. 107c(4)1].

The EURD list has been compiled 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 allows, where appropriate, the EU single assessment of the related PSURs as set out in the EU pharmacovigilance legislation [DIR Art. 107e].

The list is the relevant tool to anticipate as much as possible the PSUR-related activities, while respecting that national competent authorities can request the submission of PSURs for nationally authorised products at any time [DIR Art. 107c (2)]. The list is a living document, i.e. it can be amended whenever considered necessary by the PRAC, CHMP or CMDh in response to the emergence of relevant new safety information, newly authorised substances and requests received from the marketing authorisation holders as defined in [DIR Art 107c(6)]. Substances can be added, but also removed, as appropriate.

2. History and development of the EU Reference Dates list

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

The NCAs and the EMA worked closely in order to compile the EURD list. On several occasions, NCAs were requested to review the content, propose Union reference dates, PSUR frequencies and DLPs based on the risk profile as currently known for each active substance and combination of active substances (reference to GVP VII.C.3.4). In addition, NCAs were requested to state whether PSURs for products authorised under Articles 10(1), 10a, 14 and 16a of Directive 2001/83/EC as amended should be submitted for each of the active substances and combinations of active substances contained in the list based on the criteria laid down in the legislation [DIR 107b (3) (b)].

A draft version of the EURD list was published for consultation with stakeholders on 4th of April 2012 for a period of 2 months. Stakeholders, were invited to identify any compelling need for changes, on the grounds specified in the legislation [DIR Art 107c (6)]. In addition to submitting comments with relevance to the aforementioned legal provisions, MAHs were requested to indicate the date of the first marketing authorisation in the Union or alternatively whenever this was unavailable, the International Birth Date of their originator medicinal products containing the active substances and combinations of active substances.

The first publication of the EURD list took place on 1st October 2012.

[1] 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.

Following the outcome of the December 2012 EMA Management Board meeting, the single assessment of substances contained in nationally authorised products only (including products authorised through Mutual Recognition, Decentralised and National procedures), did not start in 2013. Such substances, with DLPs falling in this period had therefore been temporally removed from the EURD list. For more details, reference should be made to the cover note "*Assessment of Period Safety Update Reports for Nationally Authorised Products in 2013- 2014*", as well as the "*List of substances under PSUR Work Sharing scheme and other substances contained in Nationally Authorised Products with DLP synchronised*"[2].

The EU single assessment of substances contained in both centrally and nationally authorised products (CAPs and NAPs) with involvement of the PRAC started in April 2013.

Following the outcome of the EMA Management Board Meeting in March 2014, the single assessment of substances contained only in nationally authorised products started in January 2015.

The EURD list at present is still a dynamic document frequently updated in response to regulatory changes but also to constantly improve the clarity on the scope of each procedure and integration with the Article 57 database (XEVMPD). The Granularity and Periodicity Advisory group (GPAG) to the PRAC has been set-up in order to support these activities and to apply a risk based approach in defining periodicity and the scope of the PSUR single assessment procedures.

3. Scope of the EU reference dates list

The principles of the EURD list are included in the GVP Module VII – Periodic safety update report (VII.C.3).

The EURD list overrules the 'standard' submission schedule described in [DIR Art 107c (2)] and any conditions related to the frequency of submission of PSURs included in the Marketing Authorisation. Therefore, the EURD list is legally binding. However, this is without prejudice to the right of a National Competent Authority (NCA) or the European Medicines Agency (EMA) to request the submission of PSURs for either nationally or centrally authorised medicines, respectively, at any time.

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

MAHs should submit a PSUR for their medicinal product in accordance with the published submission deadline where it concerns an active substance or combination of active substances listed in the EURD list, even if their product is marketed in only one Member State, unless exempted from the PSUR submission e.g. generic and well-established use medicinal products.

Example: An active substance is authorised in several Member States by several MAHs, but MAH "X" has a medicinal authorised in one Member State only. MAH "X" should also follow the EURD list and the EU PSUR single assessment procedure.

Note: Active substances or combination of active substances contained in medicinal products that are authorised in one Member State only are not included in the EURD list and consequently not subject to the single assessment procedure.

Although the Legislation establishes a derogation for the submission of PSURs for products authorised under Articles 10(1), 10a, 14 and 16a of Directive 2001/83/EC as amended [DIR Article 107b (3)], the

[2] PSUR Work Sharing webpage, CMDh website: http://www.hma.eu/348.html

EURD list is also used as a way of simplifying NCA requests for submission of PSURs on the basis of concerns relating to pharmacovigilance data, or due to the lack of PSURs, relating to an active substance. More information on how to identify this information in the EURD list is provided in section 2.1.

3.1. Description of the EURD list

The following paragraphs provide a description of the different pieces of information that can be found in the EURD list and points to consider for the preparation and submission of the PSURs in accordance with the list.

3.1.1. Information important for planning and preparation of the PSUR

Each row in the EURD list defines one single assessment procedure and as such, separate PSURs should be prepared and submitted for medicinal products described under different EURD list entries. The main two columns to consult in order to determine if a specific medicinal product should be part of a PSUR single assessment procedure are *"Active substances and combinations of active substances"* and "*Are PSURs required for products referred to in Articles 10(1), 10a, 16a of Directive 2001/83/EC as amended? Yes/No*".

For products authorised under Article 14 of Directive 2001/83/EC, PSUR submissions are not required as part of a PSUSA, unless explicitly stated for a given entry.

Note: Any changes to the PSUR submission frequency, the submission date and the PSUR submission requirement for medicinal products referred to in Articles 10(1), 10a, 14 or 16a of Directive 2001/83/EC as stated in the EURD list come into force 6 months after its publication. There might be situations where *"ad hoc"* PSUR submissions would be necessary prior to the new frequency taking effect. These cases are indicated in the column *"Notes"* of the EURD list as *"ad-hoc"* requested PSURs (described below).

- **ID**

This new column refers to the procedure ID of the relevant entry. The ID is represented in the relevant PSUSA procedure numbers, id: ID: 1111; PSUSA/00001111/XXXXXX.

- **Active substances and combinations of active substances**

The names of the active substances and the combination of active substances are in English. The active substances and combination of active substances can be presented together as one entry in the list (in one line) or as separate entries. A slash ('/') is used to separate the different active substances contained in a combination, this can be a fixed-dose combination or a combination pack. A comma (',') is used to indicate that a single PSUR assessment covering the different substances and/or combinations of active substances will be produced.

Note 1: In case a specific salt, ester, ether, isomer, mixture of isomers, complex or derivative of an active substance is mentioned in the list, PSURs only for this specific salt, ester, ether, isomer, mixture of isomers, complex or derivative should be submitted. In all other cases the name of the active substance covers all salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives, as appropriate.

Note 2: In case, only the name of the acid or base is specified, medicinal products containing salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the acid or base should be considered as part of the single assessment procedure.

Note 3: MAHs should check the EURD list to determine whether a stand-alone PSUR for fixed dose combination products is required [IM Article 34 (7)].

Note 4: If a specific fixed combination medicinal product is not listed on the EURD list, the MAH should inform the Agency. PSURs should not be submitted according to the EURD list entry specific to one or more individual components of the fixed dose combination.

Note 5: In some cases different PSUR single assessment procedures should be followed for medicinal products containing the same active substance or combinations depending on different indications, routes of administration, dosage forms and dosing regiments [IM Article 34 (6)[3]]. In such cases, the active substance or combination of active substances appears several times in the list including in brackets the defined scope that should be covered by the PSUR (e.g. PSUR for "topical formulations" versus PSUR for "oral formulations"). MAHs should check this information to determine whether different PSURs should be submitted for medicinal products containing the same active substance [IM Article 34 (6)]

Note 6: Marketing authorisation holders should follow the EURD list entry, which is most specific to a given medicinal product (e.g. in case the general entry *"bacterial lysates"* exists but also a separate entry listing the specific bacteria *"bacteria lysates of haemophilus influenzae, klebsiella ozaenae, klebsiella pneumoniae, moraxella catarrhalis, staphylococcus aureus, streptococcus pneumoniae, streptococcus pyogenes, streptococcus viridans vaccine"*, the more specific entry should be followed for medicinal products containing the latter specific composition of active substances).

Note 7: Entries of herbal medicinal products are reflected with the scientific Latin plant name, followed by the Latin plant part or other terms specifying the entry (e.g. oral use) as relevant. Entries for herbal medicinal products are applicable for all types of medicinal products containing the respective plant, including extracts, tinctures, teas, powders etc. if not otherwise specified in the entry.

- **European Union reference date (EURD)**

The European Union reference date corresponds to the 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)]. The term "Not available*" is indicated when the EURD has not been provided during the various rounds of consultation on the EURD list with the NCAs and the MAHs.

- **PSUR Submission Frequency, Data Lock Point and Submission date**

The PSUR submission frequency and the DLP (cut off point for preparing your report) drive the submission schedule of the PSUR.

Note: In case a single assessment procedure for an active substance or combination of active substances is occurring for the first time, it is anticipated that not all PSURs which will be submitted will cover the period indicated in the EURD list. In such cases, MAHs should cover in their PSURs the period between the DLP of the last PSUR that has been submitted (e.g. PSUR submitted at national level or as part of a PSUR Work-sharing procedure) and the DLP in the EURD list.

The submission date (according to the timelines defined in GVP Module VII, Section A) is the deadline that must be followed by the MAHs.

[3] Any 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".

In addition, the columns "*Next DLP*" and "Next Submission Date" are published for active substances or combination of active substances with a PSUR frequency of up to 6 months. This is to support predictability for stakeholders in terms of PSUR-related activities.

It is important to highlight that given its objectives (see section 1. Introduction) and the risk-based approach underpinning the PSURs submission frequencies and DLPs, the EURD list can deviate from the 'standard' PSUR submission schedule defined in the legislation [DIR Art 107c (2) (b)].

- **Are PSURs required for products referred to in Articles 10(1), 10a, 16a of Directive 2001/83/EC as amended? Yes/No**

This column indicates whether products generally subject to the derogation from routine PSUR submission (products authorised under Articles 10(1), 10aand 16a of Directive 2001/83/EC) are nevertheless requested to submit a PSUR and be part of the single assessment procedure.

In such a case, the obligation to submit PSURs for MAHs of the products containing the same active substance or combination of active substances authorised under different legal basis than those specified above (i.e. not subject to the derogation) remains.

For products authorised under Article 14 of Directive 2001/83/EC, PSUR submissions are not required as part of a PSUSA, unless explicitly stated in a given entry.

- **Publication Date**

The column "*Publication date*" includes the date that the substance or combination was first published in the EURD list. This date is subsequently updated to reflect any subsequent publication of changes to that PSUR submission frequency and/or DLP.

- **Notes**

This column is used to communicate details about the active substance or combination of active substances and/or the procedure that are not captured in other fields such as: requests for "ad-hoc" PSUR, publication date of the "Next DLP", date that there was an amendment in the active substance name or the requirements for submission of PSURs for products referred to in Articles 10(1), 10a, 16a of Directive 2001/83/EC as amended.

3.1.2. Information important for the submission of the PSUR

The fields described below have been included in the EURD list to facilitate the submission of the PSUR(s). For more details on the submission process please refer to the page Periodic safety update reports: questions and answers in the EMA Website.

- **Procedure number of the PSUR single assessment**

To facilitate the submission process all the entries and procedures in the EURD list are assigned a procedure number to ensure that all PSURs subject to a given procedure are submitted with a common identification number. The assigned procedure number should be included in the cover letter sent to EMA and NCAs. The format is as follows: "PSUSA/00000000/YYYYMM", where "PSUSA" indicates that the procedure is a single assessment of PSURs, the eight digit number corresponds to a unique identification number covering only one entry in the EURD List, and the combination "YYYYMM" corresponds to the year and month of the DLP as published in the EURD list for the given active substance or combination of active substances.

For active substances or combination of active substances with a PSUR frequency of less than one year, a procedure number is usually published for both the DLP and the "Next DLP".

- **PRAC representative of the PSUR single assessment procedure and (Lead) Member State of the PSUR single assessment procedure**

A PRAC Rapporteur and Member State are appointed to lead a PSUR single assessment. Please refer to the page Periodic safety update reports: questions and answers (question 2) in the EMA Website for the role of the PRAC Rapporteur and the (Lead) Member state in the submission process and the procedure.

- **"CAP" and "NAP" columns**

In order to facilitate the identification of procedures containing centrally and/or nationally authorised substances, the extra columns "Centrally Authorised Product (CAP)" and "Nationally authorised product (NAP)" have been added in the EURD list. Please also refer to the page Periodic safety update reports: questions and answers (question 3) in the EMA Website for more information on how to use this information in relation to the submission requirements.

3.2. Maintenance of the EURD list

The EURD list is usually revised on a monthly basis and published on the EMA website the week following the CHMP and CMDh plenary meetings. Updates made to the EURD list when adopted by the CHMP and CMDh following consultation with the PRAC are highlighted in colour in order to highlight the changes to stakeholders. Changes may also be highlighted in column "Notes", as necessary.

In particular cases corrections to a given revision of the EURD List might be needed. These changes are listed in a cell on the top of the EURD List. Substances or combination of active substances deleted from the EURD list are listed in the table "Removed entries" including the month the entry is removed with a brief justification.

4. Submission of requests for amendments of the EU reference dates list

The EURD list is a living document which is amended as appropriate to reflect any changes required by the CHMP and CMDh after consultation with the PRAC:

- in response to any pharmacovigilance concerns, outcomes of referrals, on-going PSUR assessments, safety variations, line extension etc. that impact on PSUR submissions;
- in order to achieve international harmonisation;
- to avoid duplication of assessments [DIR Art 107c (6)].

Amendments of the EU reference dates list may consist of amendments to already existing active substance/combination of active substances, or addition of new active substance/combination of active substances. The requests have to be made using the specific template published on the EMA website "*Template for a request for amendments to the European Union reference dates list*", and should be addressed to EMA through the EURD list mailbox EURDList@ema.europa.eu. For requests to achieve international harmonisation, please see below the "*Note related to the requests for alignment of DLPs with the International Birth Date (IBD)")*. Any enquiry on the EURD list may also be sent to this mailbox.

To ensure all requests are correctly tracked, stakeholders should complete the fields in the dedicated template and use the following convention for the e-mail subject:

EURD list | Type of request {addition/amendment/enquiry} – active substance or combination of active substances concerned

The template consists of a WORD form: the relevant fields should be completed according to the type of request. Instructions for each field are provided below.

"Request details"

Type of request: *Select the type of request from the drop-down menu (i.e.: request for addition, amendment, etc.)*

EURD reference date: *enter EURD reference date, if applicable*

Name of active substance or combination of active substances: *Copy the name as included in the EURD list, if applicable, or enter proposed active substance or combination of active substances.* ***Please only enter 1 request per form.***

Grounds for request: *Select the category from the drop down list of options based on DIR Article 107c (6)*

Please provide the list of relevant authorised medicinal products from Article 57 database, stating the product names and EV codes in the email. If more than 10 EV codes are concerned, please provide the product names and EV Codes in an Excel spreadsheet, one EV Code per cell and attach it in the email along with the form.

Please note that each EURD list amendment is only valid 6 months after its publication. Requests may need consultation with Member States, PRAC, CHMP and/or CMDh and therefore will take time before publication. Please take this into consideration for understanding/planning timelines for amendments.

Note related to the requests for alignment of DLPs with the International Birth Date (IBD) of the originator product authorised through the centralised procedure instead of the European Union reference date (EURD):

- Until the product is authorised in the EU (i.e. until the marketing authorisation is granted by the European Commission), such requests should be addressed by email to the relevant EMA product lead for the initial Marketing Authorisation);
- When the product has been authorised (i.e. the marketing authorisation has been granted by the European Commission), such requests should be addressed to the EMA via the EURD list mailbox <EURDList@ema.europa.eu>.

5. Reminder

MAHs are reminded of their obligation to submit information to the European Medicines Agency on authorised medicines and keep this information up-to-date, pursuant to Article 57(2) of Regulation (EU) No 726/2004. This is a legally binding requirement from the EU pharmaceutical legislation. The Agency uses this information to support the analysis of data, regulatory activities and communication.

For the purpose of the EURD list, the information in Article 57 database supports the assessment of requests for amendments and addition of new active substances in the EURD list and is the basis to define products being part of a single PSUR assessment procedure.