EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Publication of :

- the List of Union reference dates and frequency of periodic safety update reports ("EU reference dates list")
- the List of active substances subject to worksharing for signal management

Sixth Stakeholders Forum on the implementation of the new Pharmacovigilance legislation, 8 November 2012

Presented by Kelly Brown – EMA Pharmacovigilance and Risk Management Sector

Highlights

PART I – The EU reference dates list

- What is the EU reference dates list?
- What are the objectives of the EU reference dates list?
- Application of the EU reference dates list
- Maintenance of the EU reference dates list

PART II – The List of active substances subject to worksharing for signal management

- What is the list?
- What are the objectives?
- Preparation and Maintenance

Final note

PART I

The EU reference dates list

What is the EU reference dates list?

- DIR Article 107c (paragraphs 4 and 7), and REG Article 26(g)
- Comprehensive list of active substances and combinations of active substances (regardless of their type of MA) for which PSUR shall be submitted as determined by the CHMP/CMDh after consultation of the PRAC
- Created using the PSUR Work Sharing and synchronisation lists and Eudravigilance Medicinal Product Dictionary
- 4 consultation phases with NCAs and public consultation (04 Apr – 4 Jun 2012)
- Adoption by the CHMP/CMDh following PRAC consultation in September 2012
- Publication on EMA website on 1 October 2012: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/09/news_detail_001616.jsp&mid=WC0b01ac058004d5c1
- Legally binding as of April 2013 (DIR Article 107c (7)). Until then, follow currently agreed PSUR submission frequency and DLP

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1 October 2012
EMA/630645/2012
Patient Health Protection

List of Union reference dates and frequency of submission of periodic safety update reports

Related Information:

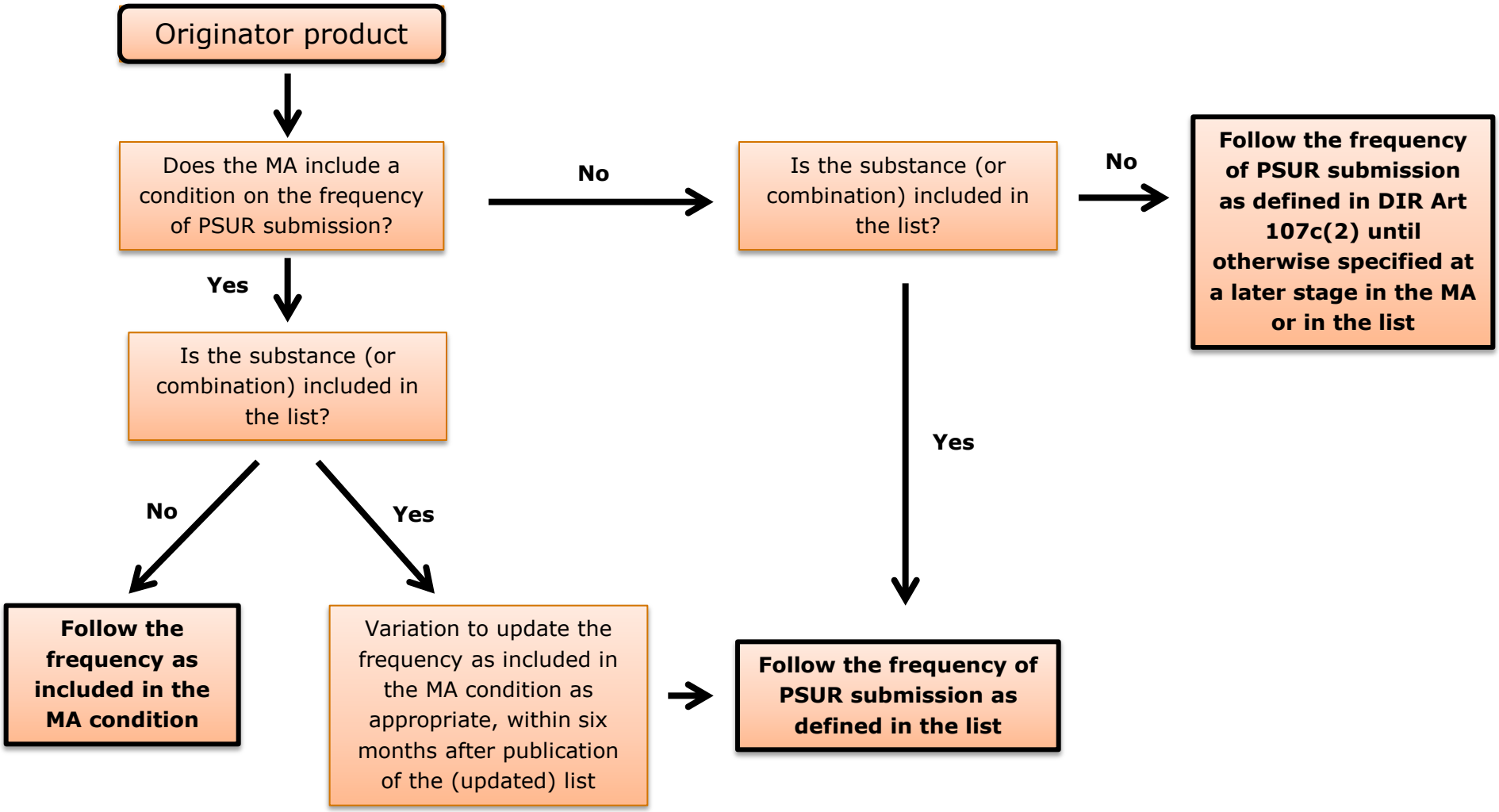
List of European Union Reference Dates - Introductory cover note for public consultation:	http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133157.pdf
Requests for amendments of the EU reference dates list	http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2012/10/WC500133160.xls

Active substances and combinations of active substances	European Union reference date (EURD) Not Available* = EURD not provided during the consultation phases	PSUR Submission Frequency	DLP	Are PSURs required for products authorised under Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended? Yes/No	Publication Date	Notes
(18f) fludeoxyglucose	14/11/1994	3 years	30/11/2014	No	01/10/2012	
l(+)biaspartate, glutamic acid, glycin, magnesium, potassium, pyridoxine	01/12/1975	13 years	01/12/2025	No	01/10/2012	
belladonna alkaloids, caffeine, ergotamine tartrate, paracetamol	Not Available*	13 years	01/01/2025	No	01/10/2012	
acetylsalicylic acid, caffeine, codeine, paracetamol	Not Available*	13 years	01/01/2025	No	01/10/2012	
caffeine, codeine phosphate, doxylamine succinate, paracetamol	07/04/1948	13 years	07/04/2025	No	01/10/2012	
gramicidin s, framycetin sulfate, polymyxin b sulfate	Not Available*	13 years	01/01/2025	No	01/10/2012	
lidocaine hydrochloride monohydrate, fludrocortisone acetate, neomycin sulfate, polymyxin b	Not Available*	13 years	01/01/2025	No	01/10/2012	

What are the objectives of the EU reference dates list?

- Harmonisation of DLPs and frequency of submission of PSUR for products subject to different marketing authorisations - Single assessment based on substances
- Optimisation of the management and assessment of PSUR for the same active substance
- The periodicity is defined on the basis of a risk-based approach
- Increase of predictability in terms of PSUR submission
- The list overrules the submission schedule described in DIR Art 107c(2)(b) and any condition laid down in the MA of the products concerned.

Application of the EU reference dates list (1/3)



Application of the EU reference dates list (2/3)

- Summary of the PSUR submission requirements (4 situations):
  - ❑ According to the EU reference dates list;
  - ❑ According to a condition of the Marketing Authorisation;
  - ❑ Submission in accordance to DIR Art 107c (2) and REG Art 28(2): Every 6 months during the first 2 years following the initial placing on the market, once a year for the following 2 years and at three-yearly intervals thereafter;
  - ❑ PSURs also need to be submitted upon request from a Competent Authority DIR Art 107c (2)

- If the active substance contained in innovator product is **not** included in the EU reference dates list : follow the submission frequency as per condition of the marketing authorisation if any, **otherwise**, follow the submission frequency as laid down in in the DIR Art 107c (2) and REG Art 28(2)

Application of the EU reference dates list (3/3)

- PSUR submission requirements for products referred to in DIR Articles 10(1), 10a, 14 and 16a

  ---→ NO PSUR REQUIRED (Art 107b(3)), UNLESS :

  - ❑ The MA provides for the submission of PSURs as a condition;
  - ❑ Requested by a Competent Authority on the basis of the grounds defined in legislation;
  - ❑ The active substance is included on the EU reference dates list and the requirement for submission of a PSUR according to the harmonised frequency is indicated:

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Active substances and combinations of active substances	European Union reference date (EURD) Not Available* = EURD not provided during the consultation phases	PSUR Submission Frequency	DLP	Are PSURs required for products authorised under Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended? Yes/No	Publication Date	Notes
abacavir	29/06/1998	3 years	31/12/2013	Yes	01/10/2012	
abacavir, lamivudine	14/11/2003	3 years	31/12/2013	Yes	01/10/2012	
abacavir, lamivudine, zidovudine	28/12/2000	3 years	31/12/2013	Yes	01/10/2012	
abarelix	Not Available*	13 years	01/01/2025	No	01/10/2012	

Maintenance of the EU reference dates list

- The information included in the list may need to be updated to reflect regulatory responsiveness to public health concerns:
  - ❑ Emergence of new information that might have an impact on the risk-benefit;
  - ❑ Change in the criteria used for the initial allocation of the frequency;
  - ❑ Active substance newly authorised;
  - ❑ Request from the MAH DIR Article 107c(6):
    - Reasons of public health;
    - in order to avoid duplications of the assessment;
    - to achieve international harmonisation.
- Requests to be made as detailed in the EU reference dates list cover note by using the published template and the EURD list mailbox (EURDList@ema.europa.eu)
- Requests will be approved or denied by the CHMP/CMDh after consultation of the PRAC
- Changes will take effect 6 months after the publication
- Q&A document under preparation taking into account recurrent questions received

PART II

The List of active substances subject to worksharing for signal management

What is the list?

- In the context of the new pharmacovigilance legislation, NCAs in collaboration with the Agency shall monitor data in EudraVigilance (EV) to determine whether there are new risks or whether risks have changed (DIR Article 107h).
- Commission Implementing Regulation (EU) No 520/2012 - Art. 22: For medicinal products authorised in accordance with Directive 2001/83/EC in more than one Member State (MS) and for active substances contained in several medicinal products where at least one marketing authorisation has been granted in accordance with Directive 2001/83/EC, MS may agree within the CMDh to appoint a lead MS and, where appropriate a co-leader, to monitor data in EV, and to validate and confirm signals on behalf of the other Member States. The CMDh may take into account RMS or Rapporteur for PSURs.
- Appointment to be reviewed at least every 4 years.
- The Agency shall publish a list of the active substances subject to worksharing for signal management together with the appointed lead Member States and co-leaders.

What are the objectives?

- To share the work and responsibilities between the Member States regarding the monitoring of data in EV and the validation / confirmation of signals identified in the EU.
- To ensure the best use of resources across the EU regulatory network (i.e. to avoid duplication of work and effort at EU level)
- To further strengthen the signal management process in the European Union for the benefits of public health.
- Remarks:
  - ❑ The list is published for information and transparency
  - ❑ Member States have joint responsibility for monitoring data in EV for products containing a substance not (yet) included in the list.

Preparation and Maintenance of the list

- Launch of several calls for volunteers to act as lead MS to monitor data in EudraVigilance (EV), and to validate and confirm signals on behalf of the other Member States
- Subset of the EU reference dates list (NAP/MRP/DCP substances only)
- List adopted by PRAC and CMDh in September 2012
- List published on EMA website on 05/10/12 (EMA/621070/2012): http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000199.jsp&mid=WC0b01ac05800250b3
- Plan for the future: further calls for lead MS for unallocated substances and for co-leaders

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5 October 2012
EMA/621070/2012
Patient Health Protection

List of active substances subject to worksharing for signal management

Introduction:

For medicinal products authorised through the national, mutual recognition or decentralised procedures in more than one Member State and for active substances contained in several medicinal products where at least one marketing authorisation was obtained through the above-mentioned procedures, the legislation foresees that a lead Member State, and where appropriate a co-leader, may be appointed to monitor data in EudraVigilance, and to validate and confirm signals on behalf of the other Member States.

The list below shows the active substances for which a lead Member State has been appointed so far. It was prepared on a voluntary basis and was adopted by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human in September 2012. The Agency provides appointed lead Member States with reaction monitoring reports from EudraVigilance for the substances allocated to them.

A number of substances have not yet been allocated and will be added to the list when lead Member States are appointed for them. Meanwhile, all Member States have joint responsibility for monitoring those medicines they have authorised. Co-leader appointment will also be considered at a later stage. Therefore this list is expected to be updated on a regular basis.

References:

Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF
Guideline on good pharmacovigilance practices (GVP) - Module IX - Signal management
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129138.pdf

Names of active substances or combinations of active substances	Lead Member Stat
(18f) fludeoxyglucose	France
5 fluorouracil, salicylic acid	Slovakia
abarelix	United Kingdom
abciximab	United Kingdom
acamprosate	Ireland
acarbose	Spain

Final note on the publication of the lists

- Huge achievement in terms of implementation of the new pharmacovigilance legislation
- Very good collaboration between the EMA and NCAs
- Significant input from the MAHs during the public consultation (EU reference dates list)
- Work towards ensuring more efficient use of resources aligned with public health priorities
- Increase of transparency and predictability regarding PSUR-related activities
- Regular updates of the list should provide opportunities to facilitate international harmonisation

Abbreviations

CHMP: Committee for Medicinal Product for Human Use

CMDh: Coordination Group for Mutual Recognition and Decentralised Procedures – Human

DLP: data lock point

DCP: Decentralised procedure

DIR: Directive 2001/83/EC as amended

EMA: European Medicines Agency

EU: European Union

MAH: Marketing authorisation holder

MA: Marketing Authorisation

MRP: Mutual Recognition procedure

NCA: National Competent Authority

PRAC: Pharmacovigilance Risk Assessment Committee

PSUR: Periodic Safety Update Report

REG: Regulation (EC) N. 726/2044 as amended

Thank you

Any questions?