EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Roadmap to PSUR

6th Industry Stakeholder Platform Meeting, 18th December 2015

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Issues for action highlighted by industry

- Bring Periodic Benefit/Risk Evaluation report (PBRER) spirit into everyday review/assessment practice (review assessor template c.f. ICH; publish ICH Q&A; agree/come to a common understanding as regards granularity needed in PBRERs)
- If safety topic review negative then close; if safety topic for ongoing monitoring in PSURs – justify and make time limited
- Don’t use PSUR as repository for all regulatory requests
- Make requests realistic and proportionate if included in preliminary assessment report
- Improve communications between MAH, procedure manager and Rapporteur/Lead Member State
- Consider PRAC procedure document to drive up standards and consistency

How are/will the points be addressed?

- Advisory Group for the EU reference date (EURD) list (GPAG – established)
- PRAC Assessors' training on 19/20 November with a focus on single assessment
- Review and refinement of the assessment report template (ongoing)
- PRAC/CMDh common understanding of optimal use of the single assessment for old substances – Workshop in January 2016
- Revision of the regional part of GVP VII – PSUR starting in 2016
- Additional template updates
- Joint Industry/network training end 2016/beginning of 2017

PSUR roadmap

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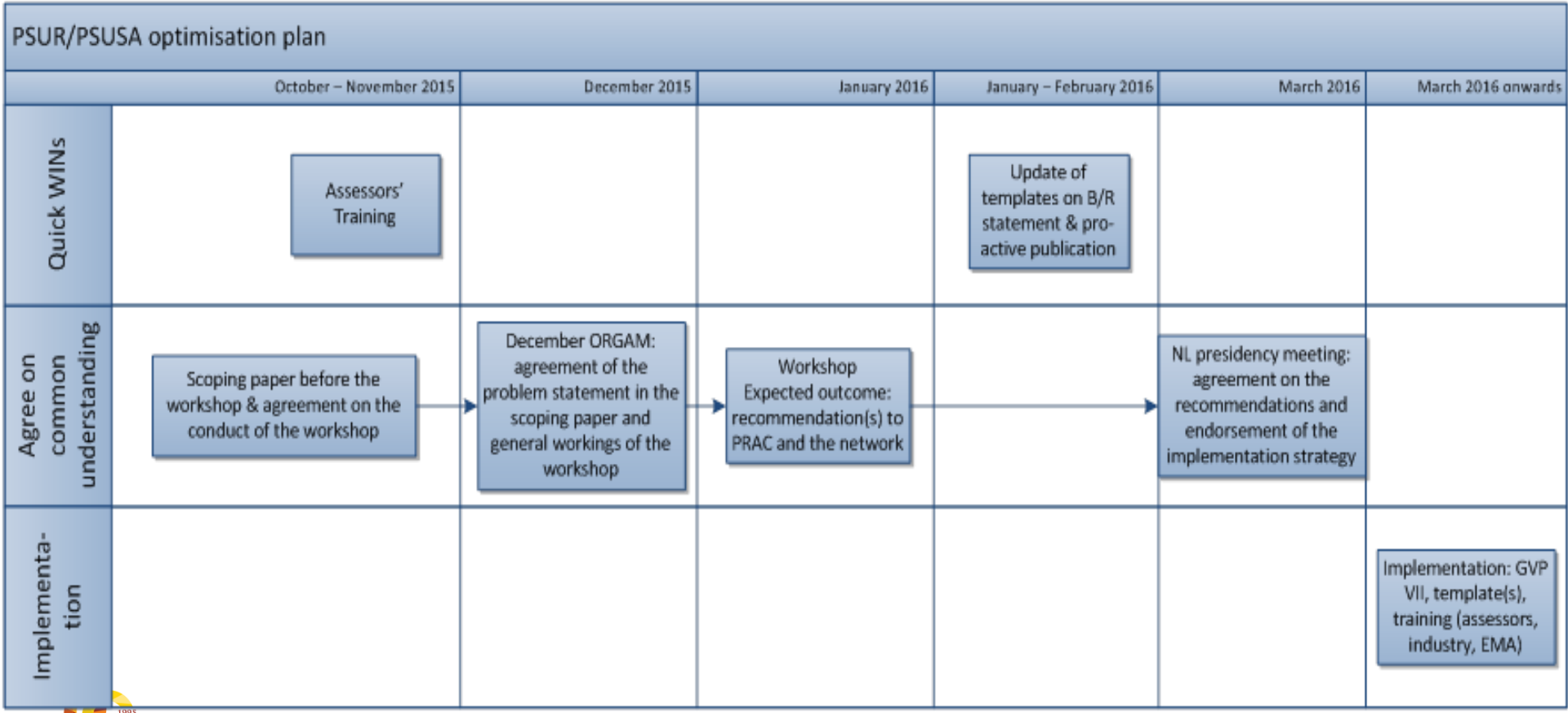


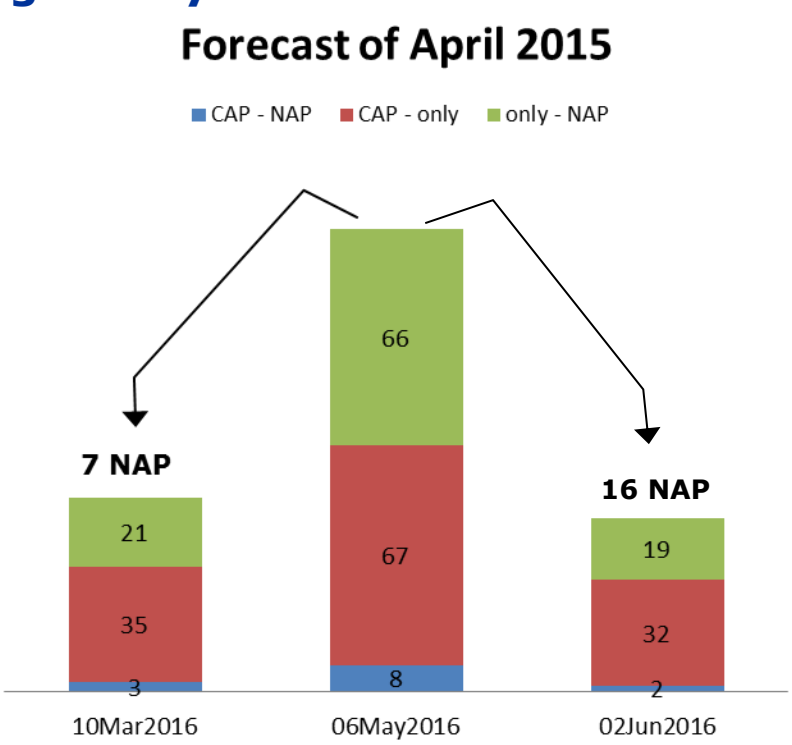
Granularity and Periodicity Advisory Group – 2015 highlights

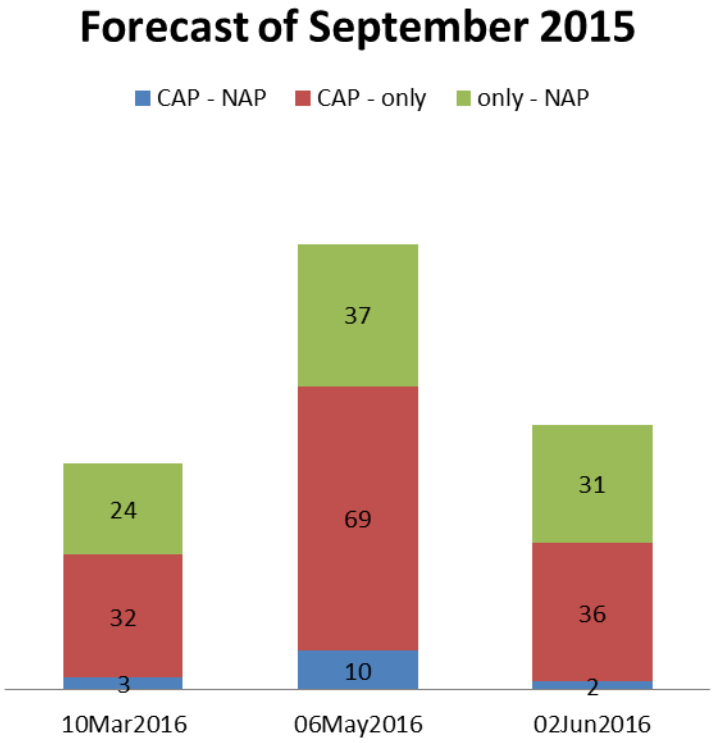
- Provides advice to PRAC for the EURD list, both on maintenance (monthly review) and rationalisation (guidance and criteria to set the periodicity) of the EURD list.
- Review of workload:
  - Change of some DLPs to avoid large peaks in PSUR submissions and assessments
  - Review of requirements for PSURs of generics, WEU etc.
  - Revision of PSUR cycle, for example for seasonal influenza vaccines
- Allergens: removed from EURD list – individual substances to return to EURD list on risk based approach
- Development of tool to assist revision and improve consistency in assignment of PSUR cycle

Exercise to change the DLPs of some NAP procedure starting in May 2016

- April 2015: Overall 141 PSUSA procedures forecasted to start in May 2016. Of these, 66 procedures were “NAP-only” procedures
- 32 procedures eligible for change (i.e. no previous international harmonisation recorded)
- 206 QPPVs were informed of the proposals to move DLPs to certain months and invited to respond only if they disagreed
- 27 QPPVs agreed, while 8 QPPVs disagreed (due to international harmonization)
- 23 procedures had their DLPs moved at the completion of the exercise
- September 2015: Overall 116 PSUSA procedures forecasted to start in May 2016. Of these, 37 procedures are “NAP-only” procedures

Feedback on the exercise to change the DLPs of some procedures starting in May 2016

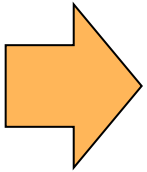




*Changes in the number of procedures observed between April 2015 and September 2015 are also accounted for by regular EURD list maintenance activities e.g. implementation of procedure outcomes, request from MAHs

Example - EURD List replacements / splittings

Active substances and combinations of active substances	PSUR Submission Frequency	DLP
calcium chloride dihydrate, glucose monohydrate	15 years	01/01/2027
calcium chloride dihydrate, glucose monohydrate, sodium chloride	13 years	01/01/2025
calcium chloride dihydrate, glucose, potassium chloride, sodium chloride	13 years	22/03/2025
calcium chloride, glucose monohydrate, magnesium chloride hexahydrate	15 years	01/01/2027
glucose	13 years	01/01/2025
glucose, potassium chloride	5 years	17/04/2019
glucose, potassium chloride, sodium chloride, sodium citrate	13 years	01/01/2025
glucose, sodium chloride	13 years	01/01/2025



Active substances and combinations of active substances	PSUR Submission Frequency	DLP
glucose (apart from glucose1-phosphate) / glucose in combination with calcium chloride and/or sodium chloride and/or magnesium chloride and/or sodium citrate and/or potassium chloride (parenteral use)	13 years	01/01/2025

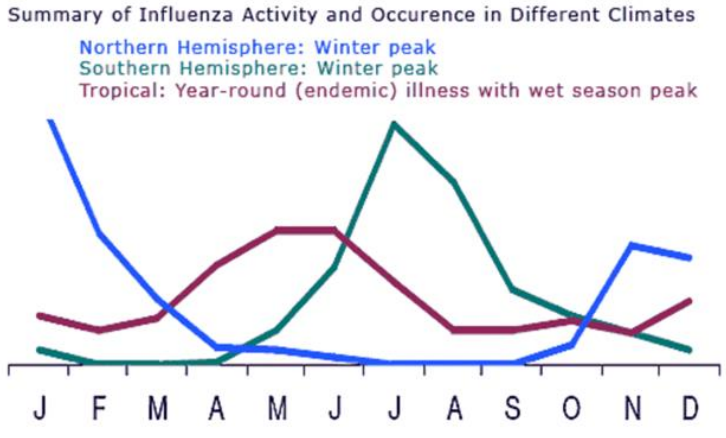
Example - EURD List replacements / splittings

- **Amitriptyline / amitriptyline, amitriptylinoxide / amitriptylinoxide (3 years, DLP 10/11/2018)→ new merged entry covering the previous entries of:**
  - amitriptyline (3 years, DLP 10/01/2015)
  - amitriptyline, amitriptylinoxide (13 years, 31/07/2025)
  - amitriptylinoxide (13 years, 01/01/2025)
- **Ivermectin → addition of new entry: two separate PSUSAs for:**
  - Ivermectin (systemic use): existing entry, 3 years, 14/04/2016
  - Ivermectin (topical use): new entry for recently approved DCP, 6 months, DLP 22/10/2015
- **Clarification of the scope midazolam (oral solution, oral tablets, solution for injection):**
  - by changing the entry name to midazolam (all pharmaceutical forms and indications apart from oromucosal solution indicated for the treatment of prolonged, acute, convulsive seizures)
  - to cover all NAPs in the EURD list including rectal solutions and solutions for infusion

Influenza vaccines - revised PSUR frequency

1-Yearly PSURs covering from 16 March to 15 March (instead of 4 / 8 monthly):

- Submission in May/June -> PRAC recommendation in October at start of influenza vaccination season
- Period will fully cover the previous southern hemisphere season (March-September) and the northern hemisphere vaccination season (Oct - Feb/March)



Adapted from: Relchelderfer PS, Kendal AP, Shortridge KF, Hampson A. et al. Influenza surveillance in the Pacific Basin. In: Current Topics in Medical Virology 1988: 412-38

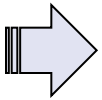
Jim Matthews (2006, April 10) Seasonal Occurrence of Influenza. Presented at Potential Engineering Approach to a Pandemic. http://www.vaccine2006.org/program.html

- Any early safety issues arising from the next southern hemisphere season could be included as late breaking information (Submission date: May/June)
- Additional data from the southern hemisphere could also be requested within the 30 days commenting phase (by mid September)

Allergens - challenges identified

- Allergen products include allergens for therapy and for diagnostic
- There is great heterogeneity of legal and regulatory framework across MSs due to different national laws
- Main issue arises from the differences in the scope of the MA which varies significantly from one MS to another:

- "Range registration": 1 registration for all allergen extracts under the same pharmaceutical form
- "Taxonomic family": 1 registration for all allergens corresponding to the same taxonomic family and presented under the same pharmaceutical form
- Individual allergen extract registration: 1 registration number for 1 allergen extract of one pharmaceutical form



- It is not always possible MAHs to relate their products in the EURD list
- One product (one licence) may fall under more than one EURD list entries, in case of range registration one product may fall under all entries
- Difficult to anticipate the products in scope of a procedures from Article 57 and fee calculation

Allergens – temporary solution

First step:

•Remove the allergen groups from the EURD list. Possible to revisit on a case by case basis a single PSUR assessment procedure for certain allergen products. Industry to be consulted.

Pros: PSUR submission for products will be able to continue at national level

Cons: No single assessment of PSURs at EU level with legally binding outcomes. MAHs will need to follow the national requirements for the submission of their PSURs

Second step:

•Reintroduction of allergens on a case by case basis

•First 3 MRP products to be re-introduced with next EURD list update