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Survey on post authorisation procedures:

Update on improvement actions

3nd Industry Stakeholder Platform Meeting / Operation of the centralised procedure - 21 April 2015

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General conclusions of 2015 EMA/Industry survey on post authorisation procedures (IBs, IIs, PSUSAs)

Overall positive feedback across 3 procedures:

- *Content, clarity of EMA pre-submission guidance;*
- *Clarity and completeness of Pre-submission queries (PQS), when used/needed;*
- *Overall quality of submission by applicants;*
- *Timeliness, level of communication and management of procedure management at EMA and from Industry;*
- *Validation and evaluation timelines;*
- *Clarity and new structure of single assessment reports.*

General conclusions of 2015 EMA/Industry survey on post authorisation procedures (IBs, IIs, PSUSAs)

Potential areas for further improvement:

- ***Post-authorisation guidance*** *– Specific suggestions for update and/further development of guidance in certain areas;*
- ***Pre-submission query service (PQS)*** *- Review timeliness of response;*
- ***Validation*** *– Consistency and communication of outcome;*
- ***Assessment Reports/ product information comments / final opinions*** *- Circulation timelines and communication of delays where they arise.*

Aim of Improvement actions

Make lifecycle management easier, predictable, faster

Regulatory simplification

- Better management of RMP lifecycle
- Submission of complex quality changes

Process simplification

- More flexibility in submission/start of Type IIs
- Earlier start of linguistic review

Increase of quality of submissions

- Get it right “first time”
- Clarity and consistency in aspects checked at validation

Increase industry awareness of existing guidance and tools

- Better engagement with MAHs.
- Update and development of new guidance

Regulatory simplification

Improvements in RMP Management

- First publication of a dedicated EMA guidance on the procedural management of RMP submissions. Expected publication by 1st June

- Aims to address MAH concerns with regards to:
  - RMP lifecycle; management of parallel submissions
  - Procedural management of changes to RMP
  - New interpretation of RMP changes classification
  - RMP submission requirements

Regulatory simplification

Improvements in RMP Management

- Main impact on MAHs
  - Decrease in administrative burden: some RMP changes currently submitted as groupings (type IIs/IBs or IBs/IBs) will be accepted within the main scope as a single submission.
    - Change in multiple due dates of submission of Final Study reports accepted in a single IB scope.
    - Submission of final study report of Cat 3 study (C.I.13, Type II) and changes to due dates of other Cat 3 study reports would not trigger grouped IB scopes.
  - Decrease in fees paid by MAHs
  - Acceptance of working combined RMP document for concomitant submissions
  - Submission of RMP closing sequence compiling all RMP changes assessed

Content of the upcoming RMP guidance

1. When should I submit a new/updated RMP?
2. When is my RMP a stand alone application?
3. What if my application does not include an updated RMP?
4. Which variation application will apply for my RMP updates?
5. Which changes can be included in an RMP update without the need for an additional variation?
6. Can I group my RMP updates?
7. How should I handle parallel RMP submissions?
8. How shall I present my RMP update?
9. Can I submit a version of the RMP after the Opinion to reflect the last minute changes made during HCMP?
10 . When should study progress reports be submitted?
11. How long after EC decision should Annex 1 of RMP be submitted to Eudravigilance?

Regulatory simplification

Submission of certain complex quality changes

- Certain complex quality cases (e.g. the introduction of a manufacturing site for FP involving changes to manufacturing process, IPCs, batch size) can involve the complex grouped submissions.
- This creates administrative burden for MAHs towards determination of the correct classification of changes, as well as complexity at and administrative burden at validation.

Ongoing initiative

- Current discussions EMA and Members States (CMD Variations subgroup) on the acceptability of some complex/consequential changes to the Finished product as a single Type II variation for a potential development of a Q&A.

Type IIs - Increase of weekly submissions and earlier linguistic review

What has been achieved?

- Monthly Type IIs were established in March 2015 for Type II variations which:
  - do not involve multiple committees (PRAC, CAT),
  - have no plenary discussions,
  - do not lead to immediate EC decision.
- 24% of Type II variations have benefited from weekly timetables allowing for a temporally more flexible outcome of the procedure (n=290 outcomes (RSI/Opinion), June-15/Mar-16)

Challenges:

- Type II variations involving the PRAC (excluding extensions of indication) currently do not benefit from weekly submissions (30% of submissions)
- 42% of weekly Type IIs have Annexes affected (n=58, June-15/Feb-16). Currently the linguistic review is performed only once a month (after CHMP).

Process simplification

Type IIs - Increase of weekly submissions and earlier linguistic review

What is next?

- To enlarge the weekly submission to variations involving the PRAC.
- To establish an additional linguistic review cycle each month, starting after PRAC, which will allow an earlier linguistic review of Type IIs where an opinion has been issued and subsequently an earlier finalisation of the procedure.
- Pilot phase of the 2nd linguistic review in May-July 2016

- **Main benefits for MAHs:**
  - More flexibility in submissions
  - Faster implementation of the Type IIs with changes to PI due to an earlier linguistic review (2 start dates per month)

Increase of quality of submissions

Reduction of validation issues and improvement of the quality of submissions

- In 44% of Type IBs and 48% of Type IIs, a request for supplementary information is issued during validation (VSI). (2015 data)
- Our aim is reduce VSI by 50%

Increase of quality of submissions

Reduction of validation issues and improvement of the quality of submissions

- Milestones:

Analysis of VSI in Type IB C.I.2 scopes. Q1 2016

- Analysis of VSI.
- Engagement with MAH to discuss challenges in preparation of submissions

Extend analysis to other types of variations. Q2 2016

- Identification of aspects for trainings, update of guidance

Webinar to MAH Q3 2016

- Presentation to MAH:
- Aspects checked at validation
- How to complete eAF
- EMA guidance
- Practical examples on common mistakes

Development of guidance on classification Q4 2016

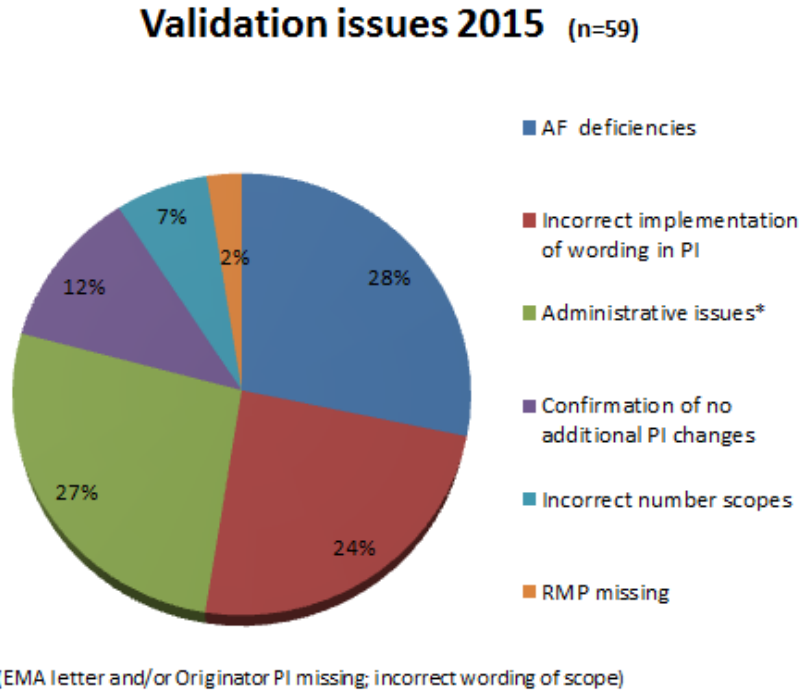
- Complement of EMA procedural and regulatory guidance

Type IBs – Reduction of validation issues and improvement quality of submissions

Analysis of VSI in Type IB C.I.2 scopes.

Q1 2016

- *C.I.2 scopes correspond to the alignment of PI of a generic/hybrid/biosimilar to the PI changes of an originator. (~13% of type IB submissions).*
- *High rate of request for supplementary information during validation in 2015 (55% of procedures)*
- *In 24% deficiencies in the submission of product information.*



Type IBs – Reduction of validation issues and improvement quality of submissions

Analysis of VSI in Type IB C.I.2 scopes.

Q1 2016

Company	% of VSI	% Incorrect PI wording	Total 2015 procedures (n)
MAH 1	63.6%	33.3%	33
MAH 2	10.0%	10.0%	10
MAH 3	100.0%	87.5%	8
MAH 4	62.5%	25.0%	8
MAH 5	71.4%	42.9%	7
MAH 6	57.1%	28.6%	7
MAH 7	60.0%	0.0%	5
MAH 8	40.0%	20.0%	5
Other MAH (n=6)	62.5%	12.5%	8

- *Differences in %VSI across and types of deficiencies in submissions from different MAHs.*

- **Next actions**

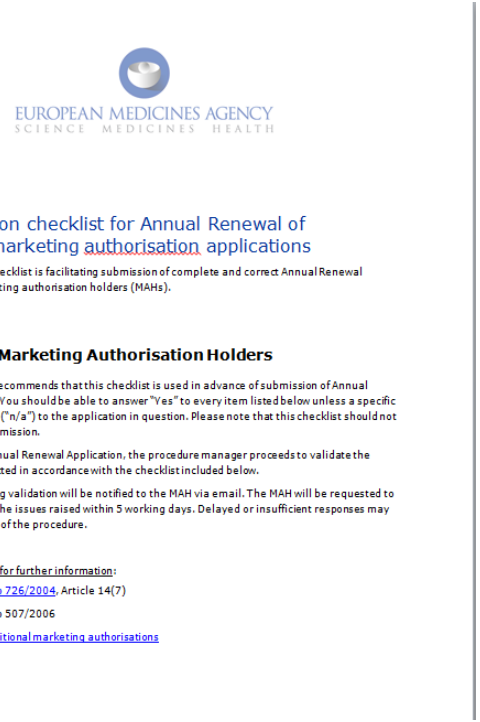
- *During May 16, EMA is approaching MAHs with higher number of submissions (n>7) and rates of VSI (>55%) to discuss the challenges faced by MAHs in the preparation of submissions.*
- *Q2 Extension of analysis to other types of variations/ scopes*
- *Q3 Webinar to MAHs*

Increase of quality of submissions

Transparency and consistency in validation

- Validation checklist for Type IAs, Type IBs published in March 2015
- Checklist for Renewals, Annual renewals and Annual reassessment published in April 2016

Next steps: Extension to additional procedures



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Pre-submission checklist for Annual Renewal of conditional marketing authorisation applications

The purpose of this checklist is facilitating submission of complete and correct Annual Renewal Applications by marketing authorisation holders (MAHs).

Guidance for Marketing Authorisation Holders

The Agency strongly recommends that this checklist is used in advance of submission of Annual Renewal Applications. You should be able to answer "Yes" to every item listed below unless a specific point is not applicable ("n/a") to the application in question. Please note that this checklist should not be included in the submission.

Upon receipt of an Annual Renewal Application, the procedure manager proceeds to validate the documentation submitted in accordance with the checklist included below.

Issues identified during validation will be notified to the MAH via email. The MAH will be requested to provide responses to the issues raised within 5 working days. Delayed or insufficient responses may affect the timely start of the procedure.

Reference documents for further information:

- Regulation (EC) No 726/2004, Article 14(7)
- Regulation (EC) No 507/2006
- Guideline on Conditional marketing authorisations

Increase awareness of guidance and tools

Development and update of EMA guidance

- An update of EMA procedural guidance on Type IBs, type IIs and PSURs was published in April to address concerns raised by MAHs during the survey and frequently asked question received by EMA PQS.
    - More clarity in procedural aspects: timelines, procedural steps/circulation of reports, management of Annexes (e.g. PSUR CAPs/NAPs), direct contact points for technical matters, eSubmissions,
    - Additional information on submission requirements: When linguistic review is needed in a type IB? When mock ups should be submitted? Can I submit a clinical study report together my PSUR?
    - Additional guidance on eAF, electronic submissions
- New modules planned: RMP and classification of changes.

Increase awareness of guidance and tools

Better engagement with MAHs.

What has been achieved?

- Regular platform meetings on centralised procedure
- Surveys on centralised procedure: Post-authorisation 2015; Initial MAA 2016
- Update of guidance, checklists,

Planned activities

- Individual discussions with MAHs on challenges in preparing submissions
- Webinar on validation of variations - Q3

Increase awareness of guidance and tools

Better engagement with MAHs.

Challenges

"The post authorisation survey revealed that 20-35 % had not used EMA guidance in the preparation of their submissions."

How can we better increase awareness of relevant guidance?

What tools would be the most effective to reach the regulatory professionals responsible for preparing of submissions?

Guidelines

Newsletters

Webinars

Recorded tutorials

Social media

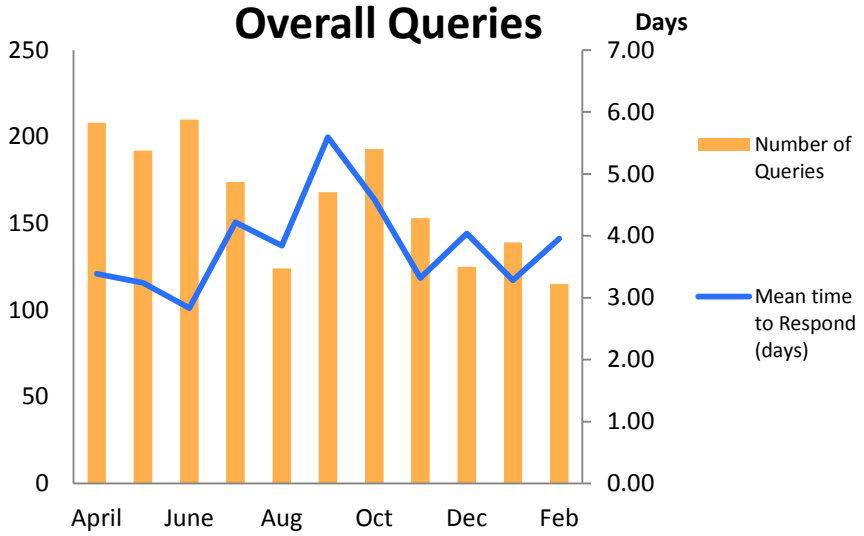
Additional points raised in the survey

Maintenance of timeliness of pre-submission query service

- Consistent number of queries handled by PQS (>160/month)
- Timeliness consistently maintained across all procedures

Experience from April 15 to Feb 16:

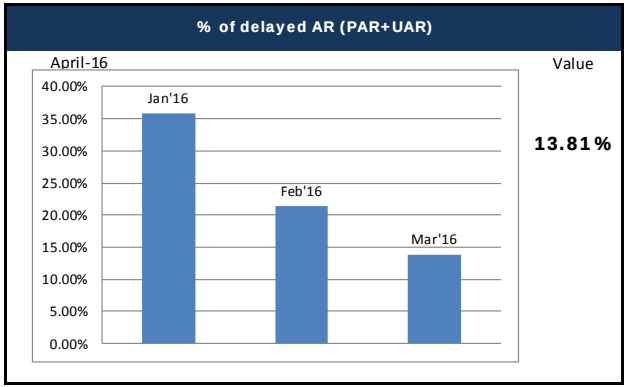
- **Mean response time: 3.87 days**
- 80% of queries replied ≤5 days; >1800 queries
- Advice provided > 5 days linked in the majority to further internal consultation



Additional points raised in the survey

Circulation of PSUR preliminary assessment reports

- 30-day commenting period for MAHs always to be ensured by delaying if needed the circulation of updated AR
- PM to liaise with PRAC Rapporteur/Lead Member State of timelines
- New commenting deadline to be proactively communicated to MAH at time of PAR
- PSUR Repository – automatic notifications to assessors of upcoming AR deadlines



PSUR Roadmap

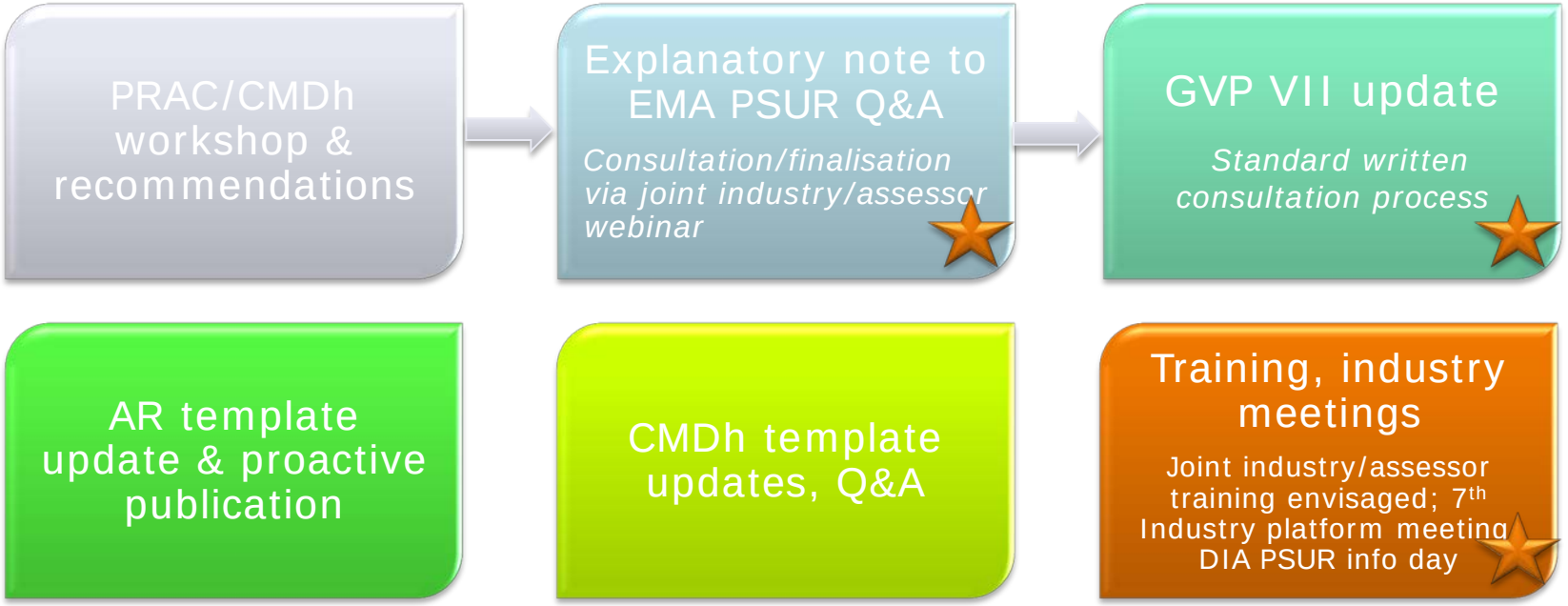
Concept of the PSUR, its assessment and role in the lifecycle of a medicinal product (critical appraisal)

Evidentiary standards in submissions and outcomes

Regulatory follow-up after procedure or for issues detected during assessment

PSUR Roadmap

PSUR Roadmap elements



Starting point - key principles (Industry focus)

- Reliance on the data (interval & cumulative) provided in PSUR → importance of data quality → prerequisite for adequate assessment
- The PSUSA is not a tool for harmonisation of product information. Consider using other procedures to reach harmonisation
- Update of safety specifications only if important new risks. Safety evaluation needs to be in context of the reference safety information (RSI) and not based on each national SmPC for a product and the RSI needs to be set into EU context.
- Improve communication on timeframe for implementation of NAPs outcomes

Starting point - key principles (Assessor focus)

- Critical appraisal should be undertaken considering the maturity of the product and its place in therapeutics
- Preparation is key, potentially reducing need for follow up; early discussion at PRAC where helpful
- New section for “Other considerations” in PRAC AR to flag important issues
- Follow up requests should be exceptional and scientifically justified (process under discussion at CMDh)
- EURD List updates should involve GPAG

Implementation timeline

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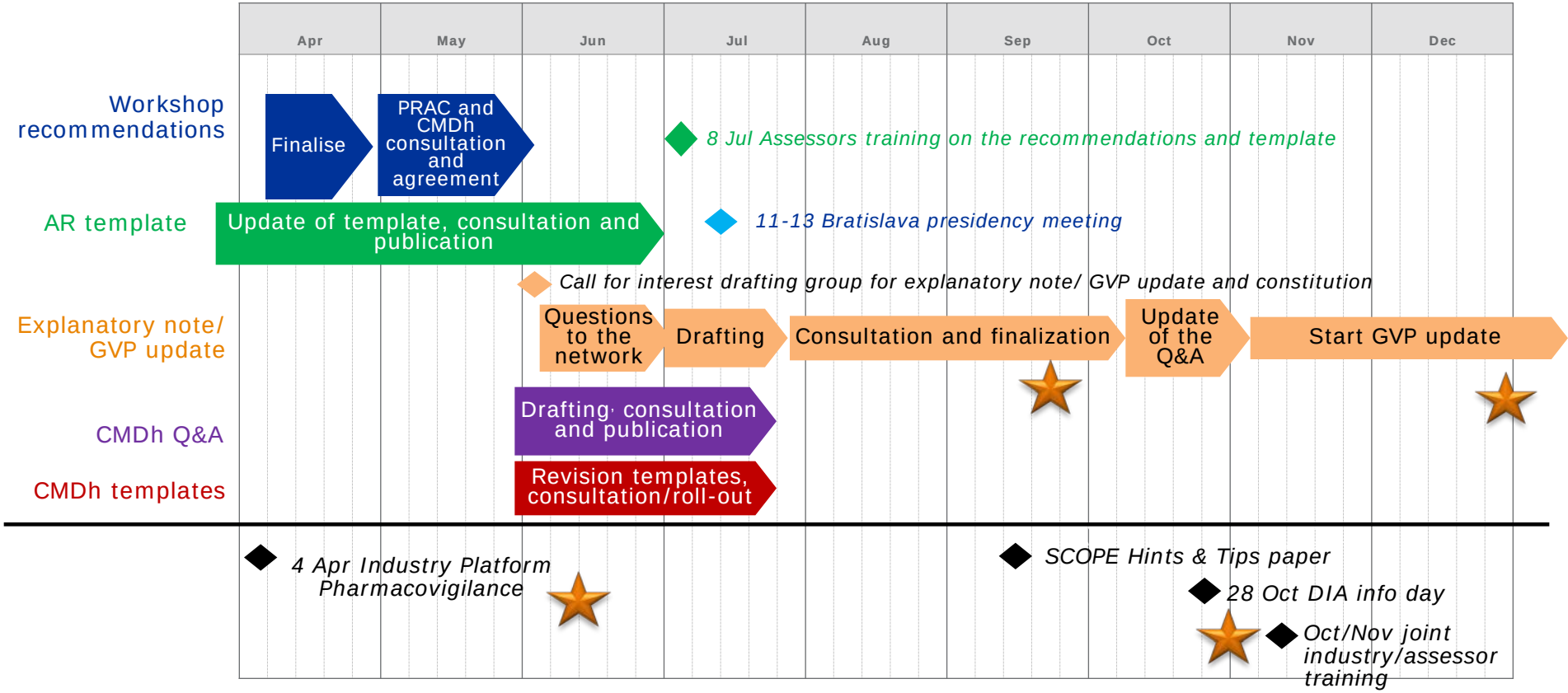

PSUR repository- Mandatory use

Key points to remember

- Use of PSUR Repository for PSUR submissions across the EU will become mandatory on the **13 June 16** for CAPs and NAPs, whether they fall under the EU Single assessment or are assessed only at national level.
- There will no longer be any requirement to submit to National Competent Authorities. Only 1 submission will be required to EMA.
- Users must be registered to the eSubmissions Gateway to submit.
- Users must have their products correctly included (legal basis!) in Art. 57.
- Submissions must be structured electronic formats (eCTD or NeeS). It is not possible to submit single pdfs via email or Eudralink.
- More info? Problems? Check eSubmissions PSUR Repository webpage or contact psurrepository@ema.europa.eu

PSUR repository- Mandatory use

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How we will facilitate transition

- General and targeted communication via Industry associations and direct mailings to QPPVs:
  - At time of advice note (DLP)
  - 1 month prior to submission deadline
- Establishment of NCA Communication Contact Points to facilitate that information is far-reaching at national level
- Webinars & Q&A sessions prior to mandatory use (see eSubmissions webpage)
- Updates of Agency webpages – EMA and NCAs

Thank you for your attention

Further information

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Back up slides

Additional details on recent PAG updates

Type IBs -Update of PAG

- The EMA procedural guidance was updated on 18th April on EMA website to addresses procedural and regulatory aspects raised by MAHs during the survey as well as frequently asked question received by EMA PQS.

Survey feedback	Update of Type IB guidance (April 2016)
More clarity on timelines for IBs	Updated information about : - Submission dates if linguistic review/no linguistic review - Circulation of Assessment report at time of notification - Full procedural steps and timelines for IBs in case of RSI during procedure.
Unclear when linguistic review is needed	New question added Q1.6 "*When do I need to submit a linguistic review?" detailing the principles and list of examples*

Type IBs Update of PAG

Survey feedback	Update of Type IB guidance (April 2016)
Need to update the guidance to eAF	Updated PAG throughout to refer to electronic submissions requirements and eAF
Frequent queries received at EMA pre submission query service	Specific requirements for submission of Annexes detailed for Type IBs with/without linguistic review.
	Further details when submission of mock-ups is needed in Type IB procedures.
Better clarity on classification of changes	New PAG module on classification of post-authorisation changes is in preparation

Type IIs Update of PAG

The procedural guidance was updated on 18/04 on the EMA website to address concerns raised by MAHs during the survey and frequently asked question received by EMA PQS.

Survey feedback	Update of Type II guidance (April 2016)
Better clarity on submission requirements	Update of Q12 and Q4 to better detail the submission requirements of PI
More clarity regarding RMP submissions is necessary	To be addressed in publication of RMP specific guidance
Better clarity on classification of changes	New PAG module on classification of post-authorisation changes is in preparation
Technical submission requirements disconnected from the type II variation PAG	Links to technical submission guidance introduced in the type II variation PAG

PSURs Update of procedural guidance

- **Update of Procedural Guidance**

Survey feedback	Update of guidance
Unclear relationship between procedural timetable and EURD list	Rewording of Q1.6. When do changes to EURD list become legally binging?
Unclear about acceptability of submission of study reports in PSURs	New Question (1.16): Can I submit a clinical study report together with my PSUR? - PSUR should contain narrative synopsis of studies reports completed during reporting period - Final study reports not previously assessed not acceptable within a PSUR
Unclear procedural steps in case procedure is changed to variation	Q1.18 updated to detail the management of Annexes in different scenarios of CAPs, CAPS/NAPS and NAPs only PSURS.

PSURs Update of procedural guidance

- **Update of Procedural Guidance**

Survey feedback	Update of guidance
Unclear Procedural steps for submission of RSI	New Question (1.20): How shall I submit the response to an RSI during a PSUSA?
Unclear submission of Annexes implementing the changes requested during PSUSA	Amended wording of Q21, detailing the processes CAPs only, CAPs/NAPs, NAPS only.
Lack of clarity on contact points. Based on pre-submission query service.	New questions (Qto clarify the contact points ied by adding new questions depending on the issue: During the procedure, technical submission, EURD list, fee payment, Q25