EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Procedure management of variations

Process changes made and current challenges

Presented by Alberto Ganan and Iordanis Gravanis on 24 April 2015
Procedure Management Department

# Outline

- Pre-submission query service
- Process changes for type IB variations and experience to date
- Process changes for type II variations
- Current challenges

# The role of PM in variations

The Procedure Manager (PM)

- is the main contact point to MAH in post authorisation procedures
- is appointed upon submission of the post-authorisation procedure
- is responsible for the management of the procedure ensuring compliance with procedural regulatory requirements
- ensures the involvement of additional expertise in complex cases, where therapeutic area oversight is needed
- provides regulatory and procedural advice at pre-submission of a variation through a dedicated service: Pre-submission queries service

# Pre-submission Queries Service

## Scope

- Address regulatory procedural pre-submission queries from MAHs related to **post authorisation procedures**: IA, IB, II variations, PSUR, MA transfer, Art. 61(3), renewal, annual reassessment, extension application, PASS, Post-authorisation measure (PAM)
- Not for initial MAA. At time of eligibility a PM is assigned and can be contacted to address any pre-submission queries

## Why

- To ensure **accuracy and consistency** in the responses provided to the MAHs & to support MAHs in their submission in a **timely** fashion
- To identify areas for development or improvement of post-authorisation guidance

# Pre-submission Queries Service

## How?

- When MAHs have a question when preparing their application they can contact the Agency using one the following email addresses (when in doubt what is the applicable mailbox, email any and the query will be re-routed internally, as necessary)

IAquery@ema.europa.eu
IBquery@ema.europa.eu
IIquery@ema.europa.eu
PSURquery@ema.europa.eu
MATransferquery@ema.europa.eu
61.3.query@ema.europa.eu
renewalquery@ema.euopa.eu
Extension application@ema.europa.eu
PAMquery@ema.europa.eu
PASS.107n_q@ema.europa.eu

Email boxes reflected in the Post-authorisation guidance Q&A

- To help the EMA deal with the enquiry, the product name should be provided together with detailed information relating to the query

# Pre-submission Queries Service

## How the PQS works?

- A dedicated team of experienced PMs across the 6 B-PM services ensure **consistency, accuracy** in the advices and **record keeping**
- A number of PMs (2-3) are allocated per mailbox to ensure internal peer review of the draft responses before the advice is provided
- These PMs are experts in the corresponding procedure e.g. PM handling PSUR procedures address the PSUR queries & conduct the peer review
- When a query spans across different procedure types, any of the relevant mailboxes can be used and a consolidated response will be provided
- In complex queries further internal consultation can happen i.e. with RA, Legal, Inspection, Rapporteurs to ensure the most accurate advice
- Queries & responses are tracked in a database to ensure consistency of the responses, identify areas for improvement of the existing Q&As & issue statistics

# Pre-submission Queries Service

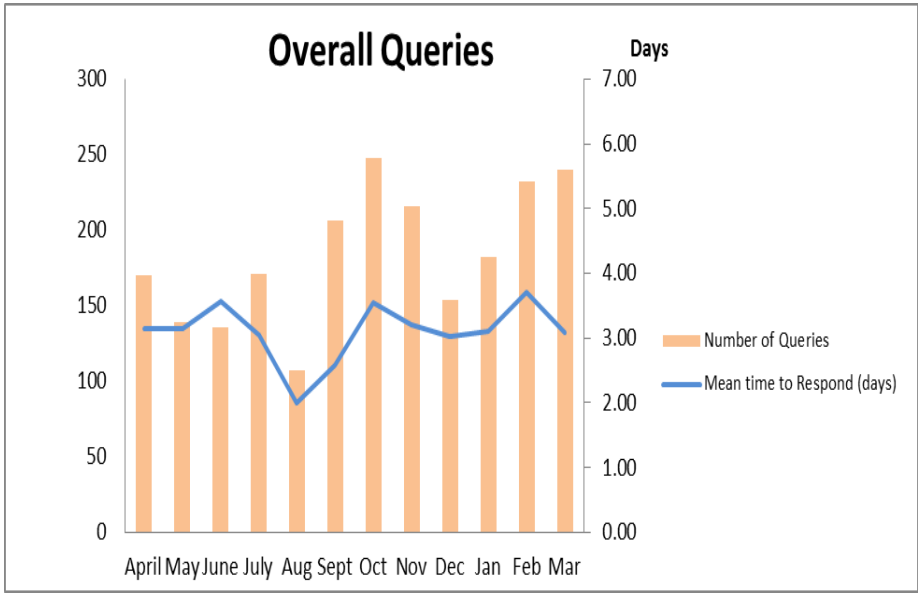
## How the PQS works?

- The Agency endeavours to provide a response within 5 working days
- With the response the MAH is notified of the contact details of the PM dealing with the request in case follow-up/clarification via e-mail or telephone is required
- Any PQS advice received should be attached to the cover letter at time of submission of the application to facilitate the validation process when applicable
- For products with a high number of upcoming post-authorisation procedures, which may require a detailed planning discussion, the PQS should be your first point of contact. The PQS colleagues will liaise with the relevant members of the product team to provide you with a consolidated responses if needed.

# Pre-submission Queries Service

Experience from April 14 to March 15 :

- **Mean response time: 3.15 days**
- 90% of queries replied ≤5 days; 2200 queries
- Advice provided > 5 days linked in the majority to further internal consultation
- Average of >180 queries per month



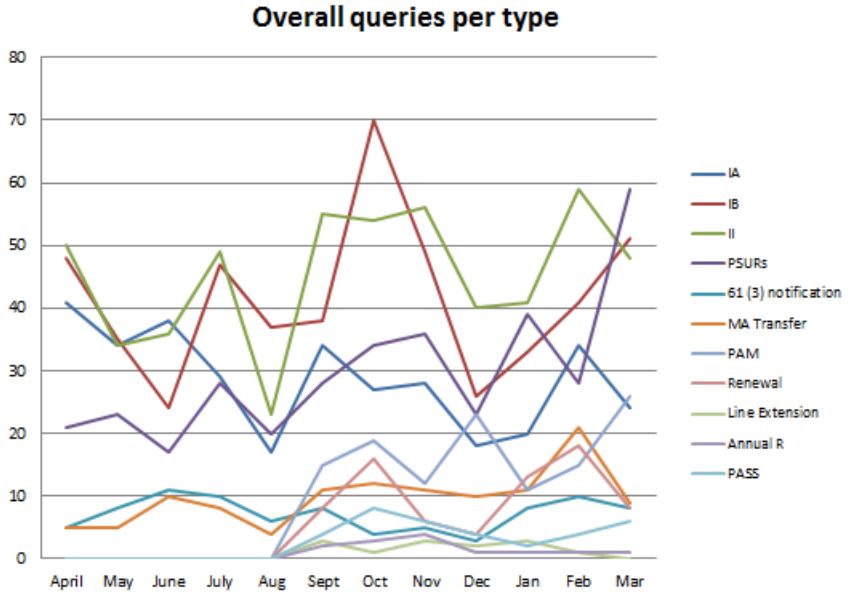
# Pre-submission Queries Service

Experience from April ‘14 to March ‘15 :

- Majority of advice sought on Type II, IB, IA variations & PSUR
- Advice on renewal, annual reassessment, extension application, PASS and PAM started in Aug 2015

What’s next:

– Review existing Q&As in light of the experience gained for future updates



# Procedural management of Type IB variations

## What is new?

- Single Report template throughout the procedure
  - Validation checklist including the classification of validations issues is shared with MAH
- Different ways of internal processing of Type IBs depending on complexity

## Main goals

- To improve efficiency by decrease of validation and processing time
- To increase first-time-correct submissions

# Procedural management of Type IB variations

## Experience since April 2014 (I)

- Faster processing of Type IBs
  - 22% reduction in Validation time in 2014 (Average time: 11,6 days vs. 15 days in 2013)
  - More than 17% of Type IB were assessed and finalised within 10 days (vs. 7% in 2013)

- Increase in “right first-time” submissions
  - 38.5% of Request from Supplementary information (RSI) at validation (vs. 90% RSI in 2012/ 2013)

# Procedural management of Type IB variations

## Experience since April 2014 (II)

- Development of new Q&A in EMA post authorisation procedural advice
  - EMA practical guidance on the application form for centralised type IA and IB variations (Dec 2104)
  - What changes will trigger new EU number(s) (additional presentation(s))? (April 2014)

## What's next?

- Maintenance and further decrease of validation and handling time.
- Further development of procedural and regulatory guidance to applicants (e.g. submissions of ASMFs).

# Procedural management of Type II variations

## What is new? (I)

- Different ways of internal processing of Type II variations depending on complexity
  - Direct involvement of EMA Product Lead (EPL) and/or Risk Management Specialist (RMS) in complex procedures, particularly evaluations requiring committee plenary discussions (e.g. extensions of indication).
- Single Assessment Report template throughout the procedure
  - Used and updated by the Rapporteur, adopted as RSI and eventually as CHMP Assessment Report

## Main goals

- Efficiency in processing and better use of resources

# Procedural management of Type II variations

## What is new? (II)

- Implementation of weekly procedure start dates for Type II variations which
  - do not involve multiple committees (PRAC, CAT)
  - do not require plenary discussion
  - do not lead to immediate EC Decision

The weekly procedure starts will apply to ~75% of submissions

Certain weeks of the year are excluded

Linguistic review remains monthly and sweeps all procedures finalised during the month

## Main goals

- Provide more flexibility to MAHs for initial submission and submission of responses

# Procedural Challenges in the procedural management of variations

- PRAC involvement
- Unexpected assessment reports
- Delayed Opinions
- Handling of parallel post-authorisation procedures
- Classification of variations

# PRAC involvement in type II variations

- In variations including an RMP submission on non-interventional PASS results
- Variations with the only aim to submit an RMP or non-interventional PASS results are PRAC-led (i.e. there is no CHMP Rapporteur assessment report)
- PRAC may occasionally be involved in relevant type II variations (e.g. ones originating from signals or PRAC requests at the conclusion of PSUR or other assessment): on a case-by-case basis and at CHMP request/as advised by the CHMP Rapporteur
- Work in progress to streamline/standardise criteria for PRAC involvement

# Unexpected assessment reports

- Procedural timetables including reports due dates and Committees involvement are provided upon start of the procedure
- Updated Assessment reports are optional but foreseen in the procedural timetable
- Unforeseen additional reports can occur occasionally
- The main goal is to address all identified/pending issues thus avoiding unnecessary additional assessment cycles

# Delayed Opinions

- Last-minute PI discussions (between MAH and Rapporteur) often delay finalisation of Opinion documents
- In more complex procedures, issues with important implications on assessment reports are sometimes settled quite late during the CHMP week (e.g. after an oral explanation)
- The EMA strives to have the PI agreed as early as possible in order not to hinder the preparation of translations by the MAH
- In the future, the adoption of Opinions outside the CHMP week should allow greater flexibility for the preparation of translations always submitted the week after CHMP

# Handling of parallel post-authorisation procedures including an RMP update

- The RMP template is being revised with the aim of simplification
- In conclusion of any procedure including an RMP update, an RMP version including only accepted changes at that point of time has to be adopted
- In some cases, minor RMP updates could be implemented in a future procedure affecting the RMP or by a proposed deadline
- Grouping of variations submitted in parallel should be considered towards having a single RMP update

# Handling of parallel post-authorisation procedures and EPAR publication

- Parallel procedures are identified by PM during validation (AF, SIAMED)
- For parallel procedures affecting Annexes handled by different PMs, PMs/PAs use the internal tracking tool to check the status of the parallel procedures and liaise internally to ensure the regulatory compliance and correctness of Annexes at opinion/notification. This issue is under review towards further optimisation
- PA checks at finalisation the status of ongoing procedures to ensure that the correct set of Annexes is adopted
- EPARs are updated on EMA website on a monthly basis. A dedicated team ensures that the update includes all EPAR changes related to the procedures finalised during the month

# Classification of variations

- MAHs are responsible for the classification of proposed changes according to the variations guidelines[1] and Commission Regulation (EC) 1234/2008, as amended.
- Practical guidance has been developed to support the implementation of the variation guidelines.
- In case of doubt, MAHs can seek regulatory advice on the classification of proposed changes by contacting the PQS service.
- In cases of unforeseen changes, the MAH can always request the Agency for a recommendation of the classification of the variation through an Art. 5 procedure.

[1]Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapter II, IIa, III and IV of Commission Regulation (EC) 1234/2008 of 24 November 2008 concerning the examination of to the terms of marketing authorisation for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant these procedures.

# Classification of variations - Submission of (non)clinical studies - I

- **Final results** of any non-clinical or clinical study (including drug utilisation studies, registries as well as meta-analyses) should be submitted as a type II variation
  - C.I.4 when changes to the Product Information are proposed
  - C.I.6 when adding new Therapeutic Indications or modifying approved ones
  - C.I.11 when (only) an Annex II condition is being fulfilled
  - C.I.13 in all other cases
- The following types of final study results are exempted
  - studies supporting quality related changes (e.g. bioequivalence/tox studies) (submit as 'B' scope)
  - studies submitted in accordance with Art.46 of the paediatric regulation (submit as PAM)
  - ERA studies (submit as IB variation)
  - imposed non-interventional PASS results (submit under Art.107q procedure) unless voluntary submission towards update of the PI (submit as C.I.4)

# Classification of variations - Submission of (non)clinical studies - II

- Examples of submissions outside the definition of ‘studies’ to be submitted as type II variations
  - Protocols
  - Status reports of studies
  - Interim results/reports, unless latest interim results of a discontinued study
  - Periodic registry reports
  - Cumulative/safety reviews, unless meta-analyses
- However, any report / (even if interim report) voluntarily submitted by MAH as type II variation would be accepted

# Classification of variations – RMP updates

- RMP update consequential to other changes (type II variation, PSUR) should be submitted with these changes and it does not justify an additional variation
  - RMP changes agreed in earlier procedures can be implemented with any upcoming RMP update
- The following RMP changes should be submitted as type IA variations
  - Changes with wording agreed/no need for further assessment
- The following RMP changes should be submitted as type IB variations
  - Changes to due dates of RMP studies
  - stand-alone RMP submissions to implement changes agreed in earlier procedures (e.g. new safety concern)
  - stand-alone RMP submissions to introduce changes which are not type II variations
- The remaining RMP updates should be submitted as type II variations
  - stand-alone RMP submissions which add or delete safety concerns, amend category 1,2 or 3 studies in the pharmacovigilance plan and/or amend (additional) risk minimisation measures

# Achievements and future expectations

Achievements

- Response to pre-submission queries within the intended timelines
- Reduction in processing time and increase in ‘first-time-right’ submissions for type IB variations
- Implementation of weekly procedure start dates for type II variations

Future expectations

- Further procedural optimisation and simplification
- Leaner RMPs in terms of both format/template and content

# Questions???