EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Management of RMP for CAPs in post-authorisation

EMA perspective

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Upcoming Q&A on procedural management of RMP submissions in post-authorisation

The Q&A is being finalised and will be published soon after the platform meeting

It consolidates and details guidance already provided on an individual basis to users of the EMA Pre-submission Query Service

The main points of the Q&A relate to questions which come up frequently in pre-submission queries and will be covered in this presentation

When should I submit an RMP (update)?

- Strictly speaking, whenever any element of the RMP is affected
- In case of a significant change to the safety profile, typically
  - New dosage form or new route of administration
  - New manufacturing process for biotechnologically-derived medicinal products
  - New indication (or significant change to current indication)
  - Clinically important changes to PI (e.g. new contraindication or warning/precaution for use)
  - New additional risk minimisation measures (or changes to existing ones)
  - Updates to Annex II conditions, PhV plan studies or PAES
- At the request of the Agency

What if I don’t submit an RMP (update)? – Pending updates

- If not submitted but warranted, an RMP update may be requested during assessment
  - The RMP update should normally occur within the procedure
  - In certain cases, the changes may be submitted as part of a subsequent RMP update
- Similarly, in case of submitted RMP update and upon request of further changes during the assessment
  - The finalisation of the RMP update should normally occur within the procedure
  - In certain cases, the changes may be submitted as part of a subsequent update
- Pending updates create a backlog and classification issues upon implementation

What submission types could include an RMP update?

- (Line) Extensions
  - New dosage form or new route of administration
- PSURs
  - Only prompted by PSUR data
  - Not allowed in case of PSUSA involving multiple products (CAPs or NAPs, creates backlog)
- Renewals
  - To clean up backlog
  - Prompted by Renewal Data
- Variations

In 194/684 (28.4%) type II and WS variations in 2015
In 157/390 (40.0%) of (non)clinical type II and WS variations in 2015

RMP update through variations

- RMP updates consequential to other changes triggering (a) variation(s) are part of these variation(s) and do not trigger additional variation
- Stand-alone RMP submissions trigger C.I.11 category variations
  - Type IA in case wording has been agreed (unusual for CAPs)
  - Type II in case of new (not previously submitted) RMP, not previously assessed changes to safety concerns, changes to additional risk minimisation measures, changes to Annex II (category 1,2) or category 3 RMP studies)
  - Type IB in case of changes to final due dates of category 1, 2, 3 studies or previously assessed changes to safety concerns
- If submitted within another variation, such changes trigger additional variations if outside the scope of that variation

What RMP changes do not trigger additional variations?

- No RMP update can be submitted outside a variation; default is C.I.11.Z (type IB) unless significant assessment is required
- Changes which can be included in an RMP update, but do not trigger additional variations:
  - Administrative or template changes
  - Updates to epidemiology or exposure information (best within a type II variation)
  - Changes to category 4 (stated) studies
  - Changes previously agreed by PRAC/CHMP (except agreed changes to safety concerns)
  - Changes to study protocols (in principle, these should be submitted as PAMs)
- When submitting an RMP update including multiple (new and/or pending) changes it is important to consider each proposed change on its own merit and decide whether it triggers a type II variation, it triggers a type IB (rarely IA) variation or it can be included as a minor change

Handling of proposed changes - example

Submission of a final study report for a category 3 study in the RMP via a type II variation C.I.13 with consequential and/or other updates of the RMP, such as:

Deletion of this study in the RMP – no need for separate variation since related to the main application;

Addition of a safety concern in the RMP following request from the PRAC as part of a PSUR assessment – 1 Type IB category C.I.11.z;

Changes to the due dates for the provision of the final study reports for 2 category 3 studies in the RMP – 2 Type IB category C.I.11.z;

Update of the RMP with new data on the clinical trial exposure – Can be implemented within the variation without the need for an additional variation.

=> Grouping of 4 variations (1 type II variation C.I.13 and 3 type IB variations C.I.11.z).

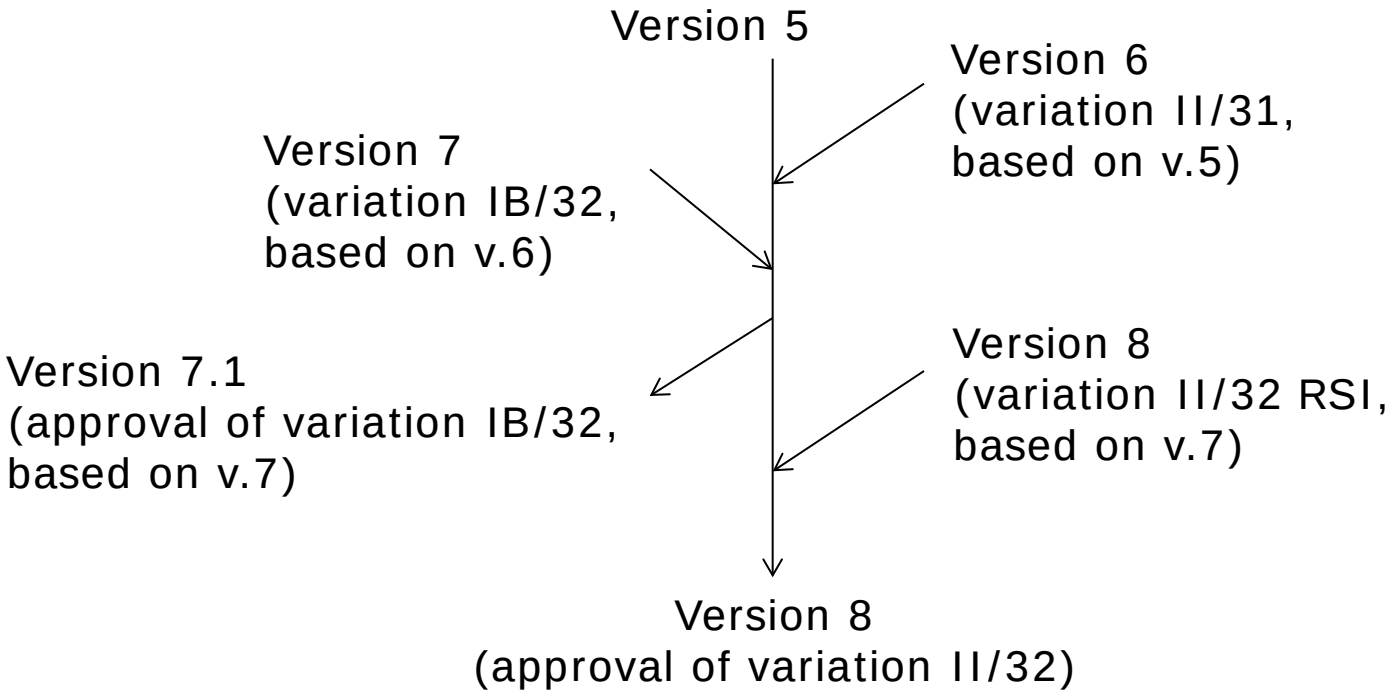
Grouping of variations including an RMP update

- RMP update in multiple variations does not suffice in principle to prompt grouping of them, **BUT** it is likely that the variations may fulfill the grouping criterion of ‘making sense to assess together’ (e.g. safety variations, but not non-clinical and safety variation)
- Grouping should not delay implementation of important changes (typically, extension of indication should not be grouped with safety variations)

Parallel RMP submissions

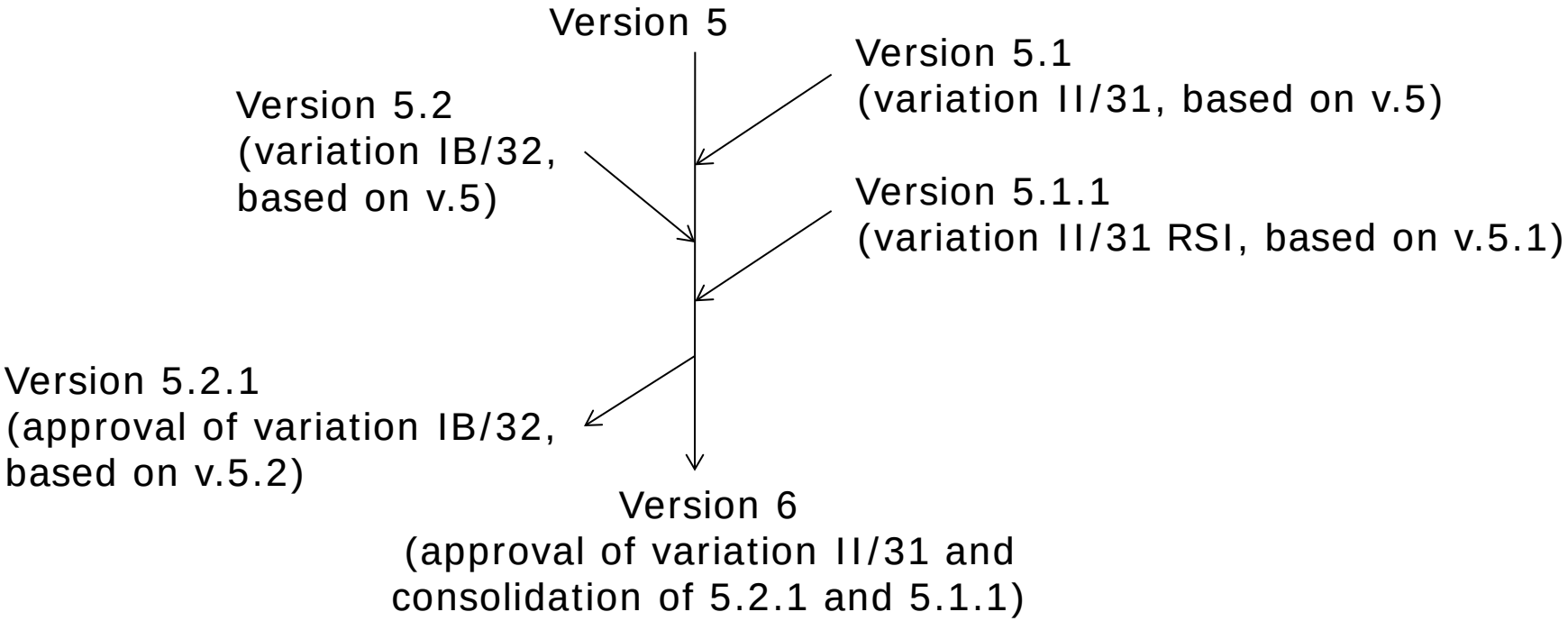
- These could be simultaneous or, more commonly, overlapping
- Simultaneous submissions could be missed grouping opportunities
- Separate or integrated versions
  - Separate versions each contain its own track changes
  - Integrated versions contain track changes from parallel procedures with changes from each procedure highlighted differently
- At the conclusion of each procedure, a clean version containing approved changes at the time of conclusion should be submitted **prior to Opinion** to become 'the latest approved RMP' and serve as basis for future submissions (unless integrated versions are being used)

RMP version number (integrated versions for parallel procedures)



Main number relates to temporal sequence and decimal relates to 'branching' clean version created for the purposes of the Opinion to serve as latest approved RMP

RMP version number (separate versions for parallel procedures)



Only main number relates strictly to temporal sequence: first decimal relates to procedure and second decimal relates to subsequent version within the procedure (including final clean one)

RMP submission requirements

- Clean version based on latest approved (separate versions for parallel submissions) or latest submitted (integrated version for parallel submissions) RMP as pdf in 1.8.2 of eCTD
- Track changes version as Word file in the separate folder 'XXXX-working documents'
- A Clinical Overview is always mandatory for a type II variation submission and it should discuss and justify RMP changes or non-submission of RMP. In case of C.I.11.b to submit a stand-alone RMP, the only objective of the Clinical Overview is to discuss and justify the proposed RMP changes.
- A closing sequence cannot be used to submit a never-before-seen RMP version (even if it is meant to consolidate agreed changes). This should be submitted prior to Opinion or with the subsequent RMP update.

Thank you for your attention

Further information

Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure

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