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Highlights from the EMA industry platform meeting held on 9 November 2015 on the operation of the centralised procedure

The following records highlights and action points from the 2nd Industry Platform meeting held on 9 November 2015 on topics presented and discussed. The meeting started with an overview of recent changes in the centralised procedure, followed by presentations and discussions on the survey on post-authorisation procedures, special aspects of variations (operational management of RMP updates during post-authorisation), labelling review (challenges in the review of mock-ups and specimens) as well as optimisation of early access tools (revision of the guidelines on Accelerated Assessment and Conditional Marketing Authorisation).

Overview of recent changes in the centralised procedure

This presentation provided a high-level overview of developments introduced in the operation of centralised procedures so far in 2015. This session introduced developments in three main topic areas: Evaluation, Process/Technical, and Labelling. The Highlights of the session are listed below; the presentation can be found here.

Evaluation

- Opinion highlights: Several new therapeutic options have received a recommendation for marketing authorisation, including several products to treat cancer as well as new treatments for hypercholesterolemia and for heart failure. Until October 2015, 4 recommendations for marketing authorisation have followed an accelerated assessment and 2 positive opinions concerned conditional marketing authorisations.
- New guidance: Two guidelines supporting early access to medicines that address unmet medical needs have been revised and released for public consultation in 2015. These are the guidelines on accelerated assessment and on conditional marketing authorisations; the finalisation is planned for 1Q16. Other important new guidance documents include the reflection paper on the evaluation of

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

new active substance status as well as the draft scientific guidance on post-authorisation efficacy studies (PAES), which was published along with the regulatory and procedural Q&A.

- Benefit /Risk methodology: Following the successful results of the pilot use of the Effects table, which was developed as part of the CHMP's project on Benefit /Risk methodologies, such tables will be routinely used in the CHMP ARs for all evaluations of MAAs and Extensions of indications starting as of February 2015, and later published in the respective EPARs.
- A brief overview of the revised process for reviewing the Risk Management Plan (RMP) during evaluations of initial marketing authorisation applications was provided. The new process, which re-fines the roles and responsibilities of the PRAC and CHMP in the review, has been implemented for all MAAs that started as of May 2015. In addition a high-level summary was provided for the ongoing revision of GVP Module V on Risk Management Systems, which is expected to be released for public consultation in February 2016.

Process / Technical

- Procedure-specific:
  - The guidance on clarification meetings on the responses to the questions raised during the evaluation was revised and is in force as of January 2015.
  - Additional submission dates are available to applicants for certain types of Type II variations
  - The new process for Renewals targeting finalisation at day 90 was implemented in September 2015.
- Updates in the post-authorisation guidance include guidance on the change that triggers a new EU number, guidance on editorial changes that can be submitted post-authorisation, and the publication of validation checklists for type IB variations.
- There have been changes in submission requirements including mandatory use of e- applications forms, the common repository and the XML delivery file for PSURs. In addition there is no longer a wet signature on CHMP Opinions and procedure related correspondence.

Labelling

- Invented names: The revised "NRG Guideline" (Rev. 6) is effective as of January 2015. The new Guideline provides further clarification of the review criteria and the decision making process in case of name similarity. Furthermore, the increased transparency in the decision making process of the Name Review Group was highlighted.
- SmPC / package leaflet: There is a new policy that allows under certain conditions combined SmPCs for different strengths of the same pharmaceutical form. A revised labelling review process during MAA evaluation is in place to allow early flagging of product information issues and that only one set of comments on the product information is sent to the applicants at D120 and D180. The general principles of acceptability and rules of procedure to include QR codes in the labelling and/or

package leaflet of medicinal products as an additional way of providing information to patients and health care professionals were published in July 2015. Since January 2015 the labelling revision following signal assessment is translated and published in all official EU languages.

- Mock-up / specimens: Significant improvements to the labelling/packaging as result of collaboration with healthcare professionals, patients and patient safety and safe medication practice organisations during the mock –up and specimen review.

Report on the outcome of the survey on post-authorisation procedures

In this session EMA and EFPIA presented the findings of the 2015 EMA-Industry survey on post-marketing authorisation procedures. Both presentations can be found here.

The survey had in scope certain post-authorisation procedures (Type IB/II variations and PSURs (CAPs only)) and reviewed the phases of each procedure, highlighting specific aspects of each (EMA Guidance, Committee reports, Request for Supplementary Information (RSI)). A particular aspect was on communication/interaction between EMA product team and Marketing Authorisation Holders.

The targeted response rate was 10% of the annual volume for each procedure. This target was met for Type IIs and Type IB variations; a 7% response rate was achieved for PSURs. During the discussions the relatively small response rates were attributed to the overall high satisfaction with these procedures.

The key survey findings from industry perspective were as follows:

- Pre submission phase: More than 90% of the respondents rated the EMA post authorisation Q&A as clear and addressing the needs of the applicants. Therefore, the Pre-Submission Queries Service (PQS) that aims at addressing applicant queries for post-authorisation submissions is not used by the majority of the applicants. When used though the responses are clear and generally timely. Validation of the submitted procedures is also generally timely.
- Evaluation phase: More than 90% of the respondents were satisfied with the interactions with the Agency; Communications were considered as timely and clear with clear contact points. The quality of the newly introduced single assessments reports was also highly rated (approx. 90 % overall satisfaction).
- Some areas for further improvement include, establishing better alerts when guidance is updated, PQS timeliness, proactive communication in case there are delays in the AR/PI comments and opinions/notifications circulation, optimisation of the PSUR process.

Feedback from EMA staff in the survey highlighted:

- Overall satisfaction in the quality of submissions received by applicants, as well as timeliness and level of communication with MAH during the procedures.
- Specific results on the type of pre-submission queries received from applicants, the most common problems identified during validation, the timeliness of circulation of ARs and finalisation of procedures were noted.

In conclusion, both respondents (EMA staff and MAHs) of the survey highlighted a high level of satisfaction across the three post- marketing authorisation procedures included in the scope of this survey, in terms of procedural management and communication. Industry welcomed the survey and expressed the wish that this will be the start of an ongoing dialogue in response, EMA agreed and stated their commitment for continuous improvement.

Selected topic on Variations: operational management of RMP updates during post-authorisation

This session focused on issues relating to the procedural management of RMP submissions in the post-authorisation lifecycle of centrally authorised products.

Industry representatives presented proposals towards procedural simplification of such submissions and their management. Some highlights of the session are listed below:

- Single substance RMP and review of this within the single substance PSUR/PBRER.
- Acceptability of multiple, unrelated RMP changes under a single type IB or type II variation (umbrella variation).
- Simplification of submission requirements for type II variations with only objective to submit an updated RMP (e.g. no requirement for Clinical Overview).
- Simplification of management of parallel RMP submissions through a single RMP document which evolves by constantly incorporating proposed and approved changes, as opposed to maintaining separate parallel versions of the RMP, one for each application/assessment procedure.
- Temporal flexibility in the submission of final RMP update related to an application, e.g. with the closing eCTD sequence for the application.
- Improvement of assessment report templates so as to clearly identify accepted changes versus ones which can be deferred to a future RMP update without the need to update the RMP before the conclusion of the procedure.

The Agency detailed the regulatory practices in the management of post-authorisation RMP submissions and especially in the framework of variations. The main principles of these practices are listed below; the presentation can be found here.

An RMP update should be submitted whenever there is a significant change to the benefit-risk balance of the product or as a result of an important pharmacovigilance or risk minimisation milestone being reached or at the request of the Agency or National Competent Authority, as specified in section V.V.5 of the GVP module 5.

- If not submitted but warranted, the RMP update may be requested during an assessment procedure and the RMP changes should normally be agreed by the time of the conclusion of the procedure; certain changes may be deferred to a future RMP update.

- A stand-alone RMP submission should be made in the form of a variation of the C.I.11 category which can be of type IA, type IB or type II as explained in the Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure; depending on the variation type, the relevant submission requirements should be followed as specified in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 (variations guideline); in particular in case of type II variations, the mandatory Clinical Overview should be used to describe and justify the proposed RMP changes and their impact on the benefit-risk balance of the medicinal product.
- Grouping of variations including an RMP update should be possible in many instances, on the grounds that e.g. safety variations make sense to be assessed together. On the other hand, safety changes cannot be grouped with an extension of indication application, unless consequential to it, because their approval will be delayed by the longer assessment timelines of the extension of indication; likewise, non-clinical and clinical variations triggering RMP updates cannot be grouped, as they will be assessed separately.
- Application of the rules for grouping of variations implies that changes triggering separate variation scopes continue to do so if these changes are submitted together; the submission will be treated as a grouped variation and not as a single umbrella variation. On the other hand, administrative or template changes, updates to epidemiology or exposure information, changes to category 4 (stated) studies in the pharmacovigilance plan, changes previously agreed by PRAC/CHMP and changes to study protocols are not considered to trigger additional variation scopes.
- Maintenance of a single, constantly evolving RMP document is acceptable, as long as proposed changes emanating from separate procedures can be identified within it; moreover, at the conclusion of any procedure, a clean version of the RMP (agreed changes from the procedure accepted while changes from other ongoing procedures removed) is requested to serve as the 'latest approved' RMP.
- A track changes version of a submitted RMP update, although not a formal requirement, is generally necessary for the assessment; submission of an RMP update with a closing sequence can only be accepted in exceptional cases and only when the actual changes have already been assessed and agreed before the conclusion of the assessment or when they are typographical corrections.

It was noted that the Agency intends to publish by the end of the year a Q&A document pertaining to the procedural management of RMP submissions within variation applications.

Labelling review: challenges in the review of mock-ups and specimens

The presentation gave an overview on the Agency's mock-up and specimen review process focusing on practical examples, available tools and areas for improvements. Industry representatives also shared their experience and challenges in handling mock-ups and specimens comments; they also raised specific labelling related questions.

Some highlights of the session are listed below; the presentation can be found here.

- Interactions with PRAC/CHMP assessors and the number of consultations with HCPs/Patients/Member States have increased.
- The review of mock-ups & specimens takes into account practical aspects, e.g. real conditions of use, posology, and storage.
- Multilingual packs: several tools/strategies are available to address readability issues and to facilitate availability of medicines.
- Definition and specific requirements for multipack presentations were presented.
- The main elements of the recently published QR codes policy were explained.

From the labelling related questions raised by Industry representatives the following was highlighted:

- The Agency is willing to provide advice on suggested changes to company design ("house style"), when possible.
- The Agency applies flexibility in terms of wording and layout for the labelling and package leaflet of generic products.
- The Agency will take steps to reflect more transparently the timelines of mock-ups review during an accelerated assessment.
- The Agency updated participants on the implementation plan of the Falsified Medicines Directive.
- There is no legal obligation for biosimilars to follow the colour codes of the originator product; the Quality Review of Documents group (QRD) will discuss further.
- The opportunity for the publication of a new technical Q&A was also identified to address a number of practical considerations/frequent mistakes.

Optimising early access tools: revision of the guidelines on Accelerated Assessment and Conditional Marketing Authorisation

This presentation provided the background and high level summary of changes on the content and process of the guidelines on Accelerated Assessment (AA) and Conditional Marketing Authorisation (CMA). Also included was a high-level overview of comments received during the public consultation on these guideline revisions; the presentation can be found here.

A variety of stakeholders (patients/consumer organisations, pharmacist, research organisations, regulatory authorities, HTA bodies and industry) have provided their comments. Points highlighted by stakeholders with regard to the Accelerated Assessment included that assessment quality must not be impacted by accelerated timelines and that products not addressing an unmet medical need could still address major public health interest. In terms of conditional marketing authorisation comments included the importance of early dialogue and engagement with downstream decision makers, as well as the need for maintenance of solid evidence. All comments provided by stakeholders will be made public by the EMA once the revision process is completed.

Additional follow-up items

Based on industry and regulator suggestions, the following should be followed up in terms of post-authorisation management:

- **Type II variations:** Review the possibility of introducing additional submission dates for Type II variations that affect the product information
- **PSURs**: Further review the PSUR process to optimise timelines and communication, timing of SmPC changes implementation and provide a simple post-procedure feedback mechanism
- **RMPs**: procedural complexities, “RMPSA” and “closing sequence” when RMP changes follow a PSUR.