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Procedure Management (E-PM) / Scientific & Regulatory Management Department (E-SR)

Highlights from the EMA industry platform meeting held on 21 April 2016 on the operation of the centralised procedure for human medicinal products

The purpose of these platform meetings between regulators and representatives of industry stakeholder organisations is to provide an opportunity for both general updates and more focused discussions on specific processes or issues to support continuous improvement, and generally to foster a constructive dialogue with industry stakeholders. This includes promoting awareness about the changes introduced in the centralised evaluation procedure, having an open dialogue and exchanges of views, and discussing ideas and proposals for continuous improvement.

The following records highlights and action points from the 3rd Industry Platform meeting held on 21 April 2016 on topics presented and discussed.

MAA evaluation under accelerated assessment: Better processes to facilitate earlier authorisation

The number of requests for accelerated assessment has increased over the last years, along with an increase in their acceptance rate by the scientific committees. EMA presented an optimised procedural framework for the assessment of marketing authorisation applications. This framework provides:

- More detailed guidance on how to justify a request for accelerated assessment
- Published timetables to streamline evaluation of requests for accelerated assessment
- More transparency in the decisions for accepting/rejecting a switch to standard assessment timelines during the procedure and
- An optimised timetable for accelerated assessment of MAAs that will be effective as of September 2016

Both Regulators and Industry participants stressed the importance of establishing an early dialogue between Regulators (EMA, CHMP/CAT and PRAC Rapporteurs) and the applicant to better prepare for an evaluation under accelerated assessment. It is crucial to achieve a mutual understanding of the data package (including RMP and GxP aspects) that will be included in the application, as well as of any supplementary data that might become available at later stages. For GxP aspects in particular, it is important to identify inspection needs as early as possible during the pre-submission discussions. Otherwise the need for an inspection can be the reason to revert to standard assessment timelines.

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Industry representatives highlighted the challenge to meet the 6-7 months' timeline for preparing the letter of intent for accelerated assessment in particular if this is based on stellar data. It was clarified that at this stage solely the expression of such intent is foreseen, for planning purposes. The actual request with scientific justification is only required 2-3 months before submission. In all cases engaging in an early dialogue supports developing a better understanding about the content of the dossier.

The following improvement actions were proposed to increase predictability throughout the procedure and to enable Industry to adhere to the reduced procedural timelines

- Timely transmission of the day 60 AR
- Provision of the draft LoQ to the applicants ahead of the CHMP plenary to allow applicants to evaluate if they can submit the D91 responses within 1 month or if a switch to normal procedure is warranted. It would also help assess the need for a clarification meeting
- Suggest/agree on potential dates for the clarification meeting prior to adoption of the LoQ to facilitate planning
- Rolling submission of meaningfully related groups of responses to LoQs to facilitate the evaluation of responses (e.g. all responses to quality questions)
- Provision of RMP core elements at the time of Opinion, and full RMP subsequent to the Opinion (day +5 along with PI translations) to allow for the internal sign-off process at company level.

Actions: EMA to investigate together with the scientific committees whether and how these proposed improvement actions can be progressed.

Initial practical experience with PRIME eligibility requests

EMA and Industry participants shared their initial experiences from the launch of the PRIME scheme in March 2016. The Agency received 18 eligibility requests (11 of which were submitted by SMEs). All requests have been of generally very good quality.

The Industry feedback was that the tools developed to support the scheme e.g. Guidance, template forms are generally clear and there were some suggestions for improvement.

- Important clarifications shared at the meeting include:
- The process is designed to be a one-step assessment of a comprehensive document; it does not provide for dialogue between the Agency and applicants before the decision on eligibility to the scheme
- One eligibility request needs to be filed per proposed indication
- Literature references should be included as part of the supporting documentation
- Although EEA establishment is not a requirement for PRIME eligibility, it remains a requirement for other support tools offered by the Agency e.g. fee incentives for SMEs and academic sponsors

The Agency noted that a substantial number of the eligibility requests concerned products which were advanced in their clinical development and yet did not have had agreement on a Paediatric Investigation Plan (PIP) or waiver. Applicants are reminded, that, according with Article 16 of the Paediatric Regulation, applications for PIP/waiver should be submitted, unless duly justified, 'not later than upon completion of the human pharmacokinetic (PK) studies', as specified in Section 5.2.3 of Part 1 of Annex 1 of Directive 2001/83/EC.

Actions: Once more experience with the PRIME scheme is gathered, it will be shared with Industry

Pre-submission interactions for MAA submission: Review of recent pre-submission interactions in the centralised procedure and best practices

To understand the benefits and opportunities that pre-submission meetings offer, EMA presented an overall analysis of the experience gained for MAAs that started in 2015. The data show that 58% of all applications for marketing authorisation had an EMA pre-submission meeting, of which 91% were applications based on a "full dossier". In the majority of the cases, questions were addressing the technical completeness of the dossier, whilst very few were focusing in preparation for the scientific evaluation. The presentations from the applicants were heterogeneous with regard to the extent and level of detail, particularly in the clinical area and the introduction of pivotal data for the application.

Industry participants agreed that PSMs are important for building an efficient path of communication with the EMA product Team and Rapporteurs, sharing knowledge about the product and facilitate the smooth evaluation of complex products. However practices may differ depending on the type of company and the complexity of the product and/or submission

Given the significant investment by both applicants and regulators it was agreed that there are opportunities for further improved engagement to add value to the dossier preparation for the evaluation. The pre-submission meetings with rapporteurs were not covered by the review. Industry expressed a wish to optimise the timing of all meetings in the preparatory phase and preferably combine them with the Rapporteurs pre-submission meetings.

Actions:

- EMA to explore whether and how the following elements can be progressed:
  - Balance between face to face meetings and written exchange ahead of the submission, also considering a more continuous dialogue during the pre-submission phase
  - Use opportunities for joint EMA/Rapporteur pre-submission meeting, as well as more coordinated pre-submission meetings across Rapporteurs;
  - Optimising the dialogue from development to evaluation and related opportunities;
- Continue sharing experiences and improvement opportunities between the Agency and industry representatives, including better definition how to demonstrate the added value of such interactions.

Updates on operations in the centralised procedure

A number of improvement opportunities were identified in the survey on post authorisation procedures presented in the 2nd platform meeting in November 2015. All improvement proposals have been implemented. The Agency provided Industry participants with a progress update.

Variations management: The Agency presented a number of simplifications that have been introduced and are expected to make lifecycle management simpler, more predictable and faster. These include:

- A simplified approach to the management of complex RMP updates: some RMP changes currently submitted as groupings (type IIs/IBs or IBs/IBs variations) will be accepted as a single variation as of the 1st of June 2016.
- A simplified approach for the handling of complex quality-related changes due to the introduction of a new manufacturing site for a finished product. Such changes could be considered for submission under a single type II scope B.II.b.1 as of the 1st of June 2016
- Introduction of a new webpage with advice on variations classification issues (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000171.jsp&mid=WC0b01ac0580a53f5f)
- Introduction of a new Q&A consolidating all procedural and regulatory aspects relating to the Risk Management Plan (RMP) lifecycle management (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000172.jsp&mid=WC0b01ac0580a53f5e)
- Extension of the weekly submissions to variations that involve PRAC effective as of April 2016.
- Piloting the introduction of a second linguistic review cycle each month, which will be starting after PRAC. This improvement is expected to provide more flexibility in submissions and will allow earlier finalisation of procedures.
- Increase of quality of submissions – get it right first time: Publication of validation checklists. To increase clarity in the aspects checked by the Agency at validation and to reduce the number of supplementary information requests -which currently ranges 45-48% for post authorisation procedures-, the Agency has published on the website the Validation checklists for the following procedures: Type IAs, Type IBs, Renewals, Annual renewals and Annual reassessment. It is expected that this will help reduce the number of issues raised at validation which represents a significant administrative burden for Industry and Regulators.
- Better engagement with MAHs - Increase industry awareness of existing guidance and tools: EMA is approaching MAHs with higher number of submissions (n>7) and rates of VSI (>55%) in the context of Type IBs C.i.2 scopes (alignment of Product Information with reference product) to discuss the challenges faced by MAHs in the preparation of their submissions.
- Improvements in PSUR management: The 30-day commenting period for MAHs is currently adhered to by delaying if needed the circulation of updated AR
- The Agency reminded that the use of the PSUR repository became mandatory on the 13th of June 2016 for PSUR submissions for CAPs and NAPs across the EU whether they fall under the EU Single assessment or are assessed only at national level. The Agency presented the planned change management activities.

PSUR process / post-authorisation guidance

Discussions at PRAC and feedback from Industry highlighted the need to reach a common understanding within PRAC and between PRAC and CMDh on certain key recurring issues with regards to the purpose of the PSUR procedure following its revision by ICH. With this purpose an action group was created with PRAC and CMDh members, to discuss the concerns and agree on joint ways forward.

The aim is to develop common understanding and recommendations to the PRAC and CMDh on four key topics:

- Concept of the PSUR and its assessment;
- PSUR presentation/content;
- PSUR assessment, conclusion and assessment report;
- Regulatory follow-up

The outcome of this reflection will be released for consultation with Industry at the end of October 2016 with the aim to finalise it by the end of the year.

Procedural support in the post-authorisation phase

The Agency is introducing a new operating model for the management of evaluation procedures for human medicines. With the new model procedure managers and procedure assistants will be allocated per product, rather than per procedure, in order to improve the co-ordination of regulatory activities with a product, particularly where multiple regulatory procedures are run in parallel for the same product. From 1st June all type II variations, extension applications, periodic safety update reports (PSURs), renewals and post-authorisation measures (PAMs) along the lifecycle of a centrally authorised medicine will be handled by a single procedure manager at the European Medicines Agency (EMA).

The Agency will notify all marketing authorisation holders directly of the names of the procedure manager and the procedure assistant who together will serve as the single EMA contact point for their medicine.

This change is made to allow the Agency to better cope with fluctuations in volumes of submissions for different procedures. This change does not affect the roles of the EPL and PM that remain the same. For more information see the public announcement

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/06/news_detail_002540.jsp&mid=WC0b01ac058004d5c1

Update on patient involvement in evaluation activities

The Agency provided with an overview of the opportunities for patients involvement in its activities and with an update from the ongoing pilot to involve patients in benefit/risk discussions at CHMP. There have been 3 cases so far and another three cases planned till the end of the pilot in the end of 2016. Once the results of the pilot are analysed the process will be integrated in the overall patients' engagement at EMA.

Introduction to the upcoming survey on initial Marketing Authorisation procedures

Following the very useful feedback obtained from the survey on post-authorisation procedures the Agency announced that a survey on initial Marketing Authorisation procedures will be launched in September 2016. The survey will cover all initial MAAs that start or reach a milestone, i.e. LoQ, LoOI, Opinion over a 6 month period (September 2016 –February 2017). The survey will be addressed to Industry, EMA and Rapporteurs. The report presenting the results of the survey and follow up action will be made publicly available in June/July 2017.