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Human Medicines Evaluation Division (E)

Highlights from the 4th EMA industry platform meeting held on the 3rd of July 2017 on the operation of the centralised procedure for human medicinal products

The purpose of these platform meetings between regulators and representatives of industry organisations is to promote awareness about the centralised evaluation procedures, foster a constructive dialogue and discuss ideas and proposals for continuous improvement.

The 4th Industry Platform meeting was held on the 3rd of July 2017. The main highlight of this meeting was the discussion about the outcome of the tri-partite survey (Rapporteurs-Industry- EMA) on Initial MAAs.

The following records highlights and action points from the meeting.

1. Initial MAA: EMA-Industry Initial MAA survey outcome

In 2013-14 the Agency initiated a major exercise whereby all the established processes for the evaluation of human medicinal products were reviewed and re-designed with the aim to simplify the existing ways of working and provide better support to its Scientific Committees and the EU Network.

In September 2016, the Agency launched a tripartite survey (EMA-Industry-Rapporteurs) on the centralised initial marketing authorisation application (MAA) procedure to collect feedback on the performance of the procedure and on the level of satisfaction with the revised ways of working. A similar survey targeting EMA and industry on centralised post-authorisation procedures was conducted in April 2015. The questions covered procedural and content related topics and queried stakeholder satisfaction

Overall, the survey showed that there is a high level of satisfaction from respondents (CHMP (Co)-Rapporteurs, EMA staff and applicants) across all phases of the procedure in terms of quality and timeliness of interactions. In terms of content, the assessments reports, questions and major objections were considered clear, well-justified and of high quality, whilst submissions were in the majority of cases adherent to the scientific advices received.

The survey identified some areas that would benefit from optimisation both from a procedural point of view and for the applicants to better prepare the quality and presentation of their dossiers.

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A detailed report about the outcomes of this survey is published on the Agency's website.

2. Strengthening the EMA support to Committees and the Network

EMA informed the audience of the on-going discussions for strengthening EMA support to Committees and the Network and its importance in the context of upcoming changes related to the preparation of the UK withdrawal from the European Union, the EMA relocation preparation and Business Continuity Planning (BCP) activities.
In that context, there would be opportunities for EMA and industry stakeholders to continue the dialogue on procedural process improvements and simplifications.

3. Initial MAA: New accelerated assessment process exchange and CMA report feedback

- The discussions focused on the experience gained with the new process of accelerated assessment (AA) and the revised supporting guidance.
- The experience with the new process (90 +30+30 days) was welcomed by applicants as it offers the opportunity for an additional list of questions (compared to the previous 120+30 days assessment schedule) and provides the opportunity to reach earlier opinions.
- The new process has also helped reduce the number of procedures reverting to standard timelines. From Sept 2016, when the new process was introduced till the time of the meeting, 9 Accelerated Assessment applications were under review (5 were approved, 3 were ongoing and 1 had switched to standard timelines).
- Industry provided positive feedback on the clarity of the guidance to request AA and EMA also gave positive feedback on the quality and timeliness of interactions with the applicants.
- Shorter timelines are challenging for assessment teams and require detailed planning. To allow for a smooth running of the evaluation process it is critical that:
  - Applicants' comply with communicated submission dates to ensure the availability of assessment teams/inspectors.
  - Pivotal/comprehensive data is not submitted as part of the responses to the List of Questions (Day 90 or Day 120).
  - Adequate and appropriate level of transparency and dialogue between EMA and the applicants is maintained from the pre-submission phase and during evaluation.
- Industry highlighted that multi-stakeholder (e.g. HTAs) early dialogue for both accelerated assessment and CMA could foster post-MA phase and patient access.

The following actions were agreed for follow-up:

- Clarification of the requirements to support a claim of unmet medical need;
- Consider how real world evidence could be used to support early access;
- Explore in collaboration with EUNeTA how conditional MAs could be used to facilitate early access of medicines.

4. Initial MAA: From benefit/risk to effects table: core tool to facilitate decision making

EMA and Industry exchanged their experience on the established Benefit Risk assessment framework and the use of the Effects Table to describe and communicate the most important benefits and risks in the specific therapeutic context, as well as the most important sources of uncertainty and variability. The main topics of the discussion included:

- Highlights of the different methodologies used by Industry varying from purely qualitative to semi-quantitative. It was noted that the role of quantitative approaches is likely to continue to evolve as more experience is gained.
- The role of the effects table as an integral part of the benefit-risks assessment framework. Issues commonly encountered with the effects table, e.g.
  - Balancing the necessary complexity whilst being concise;
  - Challenges to construct the effects table in situations such a single arm studies, multiple doses, multiple studies, multiple combinations, etc.;
  - The importance of maintaining consistency between the effects table and other regulatory documents such as the product information or the Risk Management Plan (RMP).

The following topics were identified for follow-up:

- Consider supplementing the effects table with other relevant clinical parameters, for example patient compliance and convenience, where appropriate
- Consider a common lifecycle approach to benefit - risk analysis and reflect how to incorporate post-approval safety/effectiveness data into it;
- Clarify with HTAs how the effects table could be used;
- Explore the potential use of effects table to support changes in legal status, e.g. switch to non-prescription status.
- Organise a training to industry on the effects table;

5. English version labelling review - Overview of the new process for initial MAA and data from two years' experience

The Agency provided an overview with the main improvements that were introduced two years ago in the linguistic review process for initial MAAs. The aim was to strengthen the focus on the quality of product information by ensuring better coordination of the different actors in the process, earlier identification of issues and provision of consolidated comments to applicants.

- Both Industry and Agency participants agreed that the earlier identification of issues has contributed in their timely resolution, whilst the improvement in the overall quality of comments has facilitated applicants' responses.

- Although the quality of product information submitted by applicants has improved over the years, further improvement could be made in the way benefit-risk aspects are reflected, as evidenced by the survey on initial MAAs.
- Industry highlighted the importance of receiving timely the CHMP opinions for initial MAAs and variations affecting the Annexes, as applicants need to provide the translations within 5 calendar days from the Opinion date. Given the very tight timelines, any delays create operational difficulties for companies and could have an effect on the quality of translations. Industry proposed to create different translations timetables for those variations that do not receive an immediate Commission Decision to alleviate the workload around translation preparation. Unfortunately, this is not feasible at this stage as an additional review cycle within each month would create administrative complexity for NCAs that does not outweigh the benefit.

Post-meeting note:

Applicants are advised to use the flexibility the Agency has provided with increasing the number of submission slots for Type IIs and choose those slots that allow finalisation outside the Committee weeks, thus allowing more time for preparation of translations. EMA will also consider a proposal to confirm to the companies (via e-mail) on Thursday afternoon of the CHMP the final status of the English version of the product information annexes so that the latter can start the translation work without any delay.

6. Update following the consultation with Industry associations on the "*The Best Practice Guide was adopted*"

The Agency presented the updated Best Practice Guide as developed by the HMA Taskforce following a survey and a workshop with Industry associations.

The document sets a number of principles for Industry and Regulators to follow. It stresses the importance of adhering to the communicated submission timelines and of proactively communicating any changes thereof to ensure availability of the assessment teams and therefore smooth running of evaluation procedures. Following a survey and a workshop with Industry as well as a public consultation with Industry associations the draft Best Practice Guide would be presented to HMA for adoption.

Post meeting note: The Best Practice Guide was adopted by HMA in September 2017 and is published on the Agency and HMA websites.

7. Post-authorisation:

7.1. Clinical Type IIs:

- The Agency shared data showing a small reduction in validation issues as a result of the updated Guidance on the submission requirements for Type IIs and for RMP updates. See slides for details. The audience was informed that the Agency has published a checklist to facilitate applicant submit correct and complete submissions for all Type II variations.
- The Agency provided feedback that a second monthly linguistic review for variations on weekly and alternative monthly timetables would not be feasible at this stage.

- Agreement was reached for the Agency to review its internal practices in relation to advices for RMP variations to optimise advice consistency towards MAHs.
- The industry proposal for a modular approach for submissions of RMP updates was noted and will be considered upon once more experience is gathered with the revised and simplified RMP template that was recently introduced.

7.2. Quality variations

- The Agency reported that 62% of Quality Type IIs benefited from the weekly start of procedure allowing earlier outcomes. A reduction of issues raised during validation was observed but still a significant number of quality Type IIs requires supplementary information during validation. This should be addressed by the publication of the validation checklist (see above Topic 7a).
- The Agency presented several updates of the post-authorisation guidance that should facilitate the preparation of correct submissions, these include: Guidance on wording of precise scopes; Clarification on what can be considered as non-significant in-process control or specification parameters; Clarifications of borderline issues between variations and GMP aspects for changes of sites and equipment; New guidance for introduction of new working cell banks, reference standards updates of section3.2.A.1.
- The following new simplifications for variations were presented: single variation for multiple CEP updates; acceptance of multiple new pack sizes outside an approved range; Complex changes within a single Type II for addition of new manufacturers for the active substance.
- The Agency also shared the outcome of a webinar on regulatory and procedural aspects of Type I variations addressing practical submission aspects (validation issues, eAF, dossier requirements, GMP, ASMF, CEP and update of safety information in PI for generics).
- Industry shared the challenges that different regional regulatory systems with variable requirements, approval and implementation times pose for global manufacturing and development. This often results in increased manufacturing costs and increased complexity in supply chains. Suggestions were made such as: Science and risk-based approaches to evaluate and predict product stability; use of BCS for bio-waivers as potential tools to reduce the burden associated with divergent regulatory requirements.

7.3. Post Authorisation Measures (PAMs) - Addressing issues in identifying the correct evaluation path

- The Agency informed about an improvement that would be introduced to facilitate the correct PAM submission. PAMs may fall into several categories, depending on their legal basis and the type of data to be generated. From the submissions received it is evident that there are uncertainties on the PAM classification, which increases the risk of misrouting the procedure to incorrect Committees, EMA resources or the assignment of incorrect timelines.
- The Agency informed about a new form that would be launched in September 2017 to simplify the submission process for PAMs. Upon completing the form, the MAH is automatically informed of the category of PAM and the submission type and code for the eSubmission Gateway. The MAH also receives useful procedural information, including the timetable, the EMA committees involved and the EMA resources assigned.

- The easy-to-use form will be an integral part of the regulatory submission package and its use is mandatory as of 1st September 2017.

7.4. PSUR roadmap next steps

The Agency informed about the Joint industry and EU regulatory network training on the PSUR roadmap scheduled for the 22nd of September 2017. The training aims at identifying key issues encountered by industry and regulators in the preparation of PSURS and sharing best practice to address these issues.

8. Update on the collaboration with EUnetHTA after Opinion (Joint Action 3, work package 4)

Joint production of relative effectiveness assessment (REA) of pharmaceuticals is one of the deliverables of EUnetHTA Joint Action 3 (work package 4). In a joint presentation the Agency and EUnetHTA informed about arrangements to ensure that the regulatory position is available to HTAs for the joint REA production. Once the final CHMP opinion has been adopted by the CHMP, EMA will share specified parts of the adopted CHMP assessment report to the concerned HTA bodies (HTA bodies acting as author and co-author, and WP4 co-lead partner), under confidentiality arrangements. For initial MAA this concerns the sections Problem statement; Clinical aspects; Clinical efficacy; Clinical safety; Benefit-risk balance; Recommendations. This new type of collaboration will support timely and robust joint REA production.