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European Medicines Agency

Highlight report: 12th meeting of the industry stakeholder platform on the operation of the centralised procedure for human medicines

19 June 2024

Role	Name
Chair	Alberto Gañán Jiménez
Present	Industry: AESGP: Birgit Ewert, Heike Wollersen, Klavdija Kmetic, Mihai Ionita, Oliver Hartmann. Alliance for Regenerative Medicine (ARM): Michael Werner. EFPIA: Almath Spooner, Amanda Matthews, Chloe Garay, Denis Burkhalter*, Mark Mayer, Pär Tellner*, Rebecca Lumsden*, Rodrigo Palacios*, Stephan Rönninger*. EUCOPE: Bertrand Fournier*, Lars Hyveld-Nielsen, Nasir Hussain, Nola Tewab*, Mary Ryan*, Roberta Bernardelli, Sean Byrne, Suzie Henderson*. EUROPABIO: Emilien Gantelet, Ines Guerra, Marcello Milano*, Pedro Franco*, Valentin Plouchard. EUROPHARM: Alain Verrijdt, Graeme Ladds. MEDICINES FOR EUROPE: Alexandra Vaz, Ana-Maria Gherghina, Andrew Modley, Beata Stepniewska*, Beatriz Solanas, Britt Vermeij*, Kornel Szerdi, Mechthild Sander, Nora Weitbrecht, Phyllida Duncan*, Raluca Radu. MPP Association: Andreas Emmendoerffer, Aurélie Rebuffet, Barbara Gollob, Christoph Joosten, Samuel Gavillet. VACCINES FOR EUROPE: Agnes Legathe, Andrea Iordache, Anna Czwarno, Craig Johnson, Evonne Strand, Helena Ardebrant*, Natacha Fovel, Stephane Callewaert. BfArM: Anna Nickel. EMA: Alberto Gañán Jiménez*, Alexios Skarlatos, Alexis Nolte, Andrea Taft, Andrei Catalin Spinei*, Christelle Bouygues*, Christopher Gadd*, Claudia Vicenzi, Enrico Tognana, Francesca Day*, Francisco Penaranda Fernandez*, Isabel Chicharro*, Joris Wiemer, Juan Garcia*, Lena Marletta, Leonor Enes, Madalina Duta-Mare*, Maria Bonafonte*, Maria Filancia, Marie-Agnes Heine*, Marie-Helene Pinheiro, Pascal Venneugues, Rosa Gonzalez Quevedo, Silvy da Rocha Dias, Sonia Ribeiro*, Thibaut Sauces, Thomas Girard, Virginia Rojo Guerra*, EMA scientific committees and working parties: Harald Enzmann, Sabine Straus. European Commission: Antonios Rodiadis, Lilia Luchianov, Marco Capellino, Paul Piscoi.

* In-person attendance

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This report summarises the 12th EMA-Industry stakeholder centralised platform meeting. These meetings are set up by the Agency as an exchange platform between regulators and representatives of industry stakeholder organisations aiming to foster a constructive exchange on general updates and more focused discussions on specific EMA centralised processes and issues to support continuous improvement.

1. Patient engagement, general update

EMA provided an update on the ongoing activities towards enhancing the incorporation of Patient experience data (PED) in drug development and regulatory decision making. See presentation.

EU regulators welcome PED as an important contribution to the totality of evidence and are working collaboratively to enable its broader use in regulatory decision-making. In this context, PED must be of high quality to meet regulatory requirements.

EMA has established an EU expert drafting group with members from the relevant scientific committees and working parties to work on an EU Reflection paper. It will define the main principles and framework for the regulatory use of patient experience data and is not meant to be a methodological guidance. The draft reflection paper is aimed to be released for public consultation in Q1 2025. EMA reminded that applicants can always discuss the best way to generate and collect PED on their specific product development plans through scientific advice and qualification of novel methodologies.

Industry acknowledged that EMA and the EU medicines regulatory network are taking important policy steps towards elevating patient outcomes in evidence generation and recommended that a workshop on approaches to evidence generation using PED is organised as part of the consultation of the reflection paper.

Conclusion and follow-up actions

EMA provided an update on the progress of key priority actions on PED (draft reflection paper on PED and measures to improve transparency in the submission and evaluation of PED). Industry gave a presentation on their expectations and provided examples of where the alignment of messages on the value of PED could be improved. The possibility of a multi-stakeholder workshop following the public consultation on the reflection paper was also suggested for further consideration.

2. Update on digitalisation (Product Management System)

Current product regulatory databases have a mismatch in granularity for the different products. In crisis situations, availability and supply data require reporting at the level of pack size, that will be the level of granularity also required in PMS. EMA is asking industry to pre-emptively provide package details for the Union List of Critical Medicines through XEVMPD in anticipation of their possible relevance in a crisis. See presentation.

Industry expressed concerns on the proposed approach that is considered as a transitional measure posing technical challenges to some MAHs. Industry is also concerned on whether the pack size data reported in XEVMPD will be transferred to PMS) and expressed preferred alternative solutions (e.g. creation of product entities via PMS directly).

Due to critical European Shortages Monitoring Platform (ESMP) timelines and after consideration of different alternatives, EMA clarified that XEVMPD submission is the only solution available that supports creation and maintenance of package data without jeopardising ESMP go live in Feb 2025. EMA offered the submission of pack size data only for critical medicines (10%) to limit the impact on Industry.

After the meeting, industry provided survey data on 46 MAHs reflecting that 13% have submitted the data in XEVMPD, 50% of MAHs (23 out of 46) are preparing them and 37% have not actioned yet. Industry noted on the need of further guidance and EMA is planning a webinar in July.

Conclusion and follow-up actions

A public webinar on pack size submissions took place on 11 July 2024. Further engagement with industry will take place through the established framework of interactions EMA - industry SME on PMS.

3. Update on IRIS Product Lifecycle Management roll-out

EMA made a presentation on the expected timelines for IRIS RPM for 2024 and 2025 and the level of communication and engagement with Industry. Subject to successful go-life for epic 1 (i.e. Variations, Transfers and Article 61.3) in January 2024, the EMA is working in epic 2 for the implementation by end of 2024 for the remaining post-authorisation processes for both Human and Veterinary medicinal products. The rationale for this deadline is to be ready for implementation of the new fee regulation by 1st January 2025 and to reduce the transition phase, where Industry, NCAs and EMA must work in two parallel systems (i.e. SIAMED and IRIS) for the same products. EMA communicated that plans for 2025 is to implement in epic 3 in IRIS the process for initial Marketing Authorisations for both Human and Veterinary medicinal products and any other process and/or data contained in SIAMED to be ready to decommission this system in 2026. See presentation.

EMA communicated that Industry Subject Matter Experts (SME) from industry (trade) organisations representing from both Human and Veterinary pharmaceutical industry are involved in the different epics for IRIS. Industry SMEs provide technical and regulatory input, are informed on progress development by participating in the quarterly IT system demos and participate in the UAT, etc. In addition, they are responsible to coordinate input and communication with cross Industry (trade) associations on the later, in addition to EMA communication. Impact for Industry is expected to be much higher in current epic 2, as more processes for all CAPs products will be onboarded, including NAPs products where for EMA-led processes. EMA informed that change management activities will increase in the second half of 2024 and beginning 2025 for a successful go-live and transition and presented a high level of these activities.

Conclusion and follow-up actions

It was recognised a good level of engagement with Industry for epic 1 and encouraged to maintain it in the future for new implementations. It was recommended by SMEs to take into account their limited capacity and rare interactions with EMA in order to provide just the necessary training and to develop user friendly systems to avoid unnecessary complications. Industry also recommended to develop a system to get data from IRIS in order to integrate it with their RIM systems. EMA communicated that we are working in agile and after each go-live the SMEs may propose such changes for future implementation. In addition, Industry recommended to simplify the access management for those companies with a big portfolio of products, as the current system would require extensive manual work for Industry.

4. Initiative to increase the capacity of the EU Medicines Regulatory Network (IncreaseNet)

A representative of BfArM gave a short presentation on IncreaseNET – EU4Health Joint Action on capacity building in the EU and explained its main objective to increase the number and expertise of assessors covering, in particular, work package 6 'on-the-job training & coaching'. Experienced NCAs acting as (co-) Rapporteurs in the centralised procedure will take on board assessors from other NCAs, to strengthen future collaboration and expertise across the European Medicines Regulatory Network. One of the long-term effects expected of the project is the increase in Multinational Assessment Teams (MNATs).

The interface with Industry was highlighted, i.e. that assessors from NCAs other than the appointed (co-) Rapporteurs may participate in certain meetings (e.g. pre-submission meetings).

Industry stakeholders highlighted the challenges and opportunities for the EU Medicines Regulatory Network (EMRN), including the increasing complexity of medicines and their support for a vibrant EMRN with the capabilities and capacities needed for EU's future.

Industry stakeholders welcomed the initiative to enhance on-the-job training, including participation of assessors at meetings with Industry and to expand the future capacities of MNATs. Industry would welcome progress updates over the course of the 3-year initiative. Training was also acknowledged as key to enhance regulatory capabilities. The network should also consider how to retain experienced staff in NCAs for the sustainability of the EMRN.

Conclusion and follow-up actions

Industry Associations were informed of the initiative.

5. Lifecycle management of combination products at post-authorisation

Industry associations made a joint presentation highlighting areas with challenges in the implementing of the Medical Devices Regulations with a special focus on connected combined devices and on the lifecycle management of combinations products. The main area for discussion in the meeting: labelling considerations on connected combined products. The regulators remit for digital solutions and considerations on the dossier content were agreed to be followed up in upcoming meetings.

EMA delivered a presentation concerning some of the points raised by Industry on labelling and lifecycle management. On the labelling aspects, Industry presented a case on the optional use of the connected combined product (CCP) without any claimed benefits. During the discussion of medicinal product label impact, EMA emphasised the importance to assess the absence of the impact on the quality, safety and efficacy and potential inherent risk linked to the combined use of the medicinal product with CCP, even if no benefit is claimed. Aspects such as medication errors caused by malfunctioning CCPs could result in infra/overdosing and affect the overall benefit/risk of the medicinal product and should be discussed in the submissions. On lifecycle management, the main goal was to clarify that partial GSPR compliance is a blocking issue for MAA/variations, that the Notified body opinion (NBOp) is a one-off procedure only required for new devices or major changes to the device and the inclusion of some aspects of ICH Q12 (risk-based approach), while others (i.e. established conditions) need to wait since they are not reflected in the EU legal framework. It was also recognized that there are still a number of issues under discussion with EC and NBCG-MED. The Q&A will be updated as the discussion progresses. See presentation.

EMA presentation also included a high-level update on the Variations classification guideline, where new scopes have been drafted to cover co-packed, referenced and integral devices considering the new Q&A on MDR requirements and the Guideline on quality documentation for medicinal products when used with a medical device.

Conclusion and follow-up actions

The discussion provided valuable insights and allowed for the development of a shared understanding on the potential challenges that the industry faces with regards to the lifecycle management of combination products across different aspects. It provided an insight into the issues that require further attention and discussion.

EMA to follow-up on a number of issues regarding combination products with EC and NBCG-MED. The Q&A will be updated as the discussion progresses.

6. EMA corporate website

EMA gave a presentation to show progress of its project to transition the EMA corporate website (www.ema.europa.eu) from Drupal 7 to Drupal 10. This project began in February 2022 and required a complete rebuild of the website, going live in December 2023. The long analysis, development, testing and content-migration period was necessary due to the website's complexity and unusually large size, including more than 20,000 web pages and over 250,000 documents[1]. See presentation.

EMA thanked the industry attendees for their patience while EMA and its development partner at the European Commission's Directorate-General for Informatics (DIGIT) addressed go-live bugs. The bug-fixing period ended in March 2024.

EMA explained that the transition project was still underway and that EMA and DIGIT were working on a prioritised backlog of improvements for the website. EMA highlighted three improvements planned for 2024 that are of particular importance for the website's key users, staff from the pharmaceutical industry working in regulatory science and similar functions:

- Bringing the website's search functionalities into line with key user needs and expectations
- Re-designing the post-authorisation procedure section on medicine pages
- Improving the categorisation and findability of scientific guideline documents

EMA stressed that comments, feedback and notification of errors and bugs from users are welcome at any time. It also announced that it plans to re-establish the EMA Website Key User Group later in 2024, a forum for discussion of suggestions, feedback and concerns related to the corporate website from industry associations and other key stakeholders. This group's activities have been on hold since 2020. The group's activities could potentially expand into taking part in research-, design- and development-related activities in the future, including usability and user-acceptance testing.

In its presentation, industry representatives reiterated their main use cases relating to EMA's corporate website, i.e. ensuring compliance, identifying comparators and learning about best practices. They thanked EMA for the improvements it has made to its website, including:

- more efficient searching with the new find medicine feature;
- clearer linking to paediatric-investigation-plan and orphan-designation pages on medicine pages;
- inclusion of 'new' and 'updated' statuses on what's new.

In terms of opportunities for improvement, industry representatives welcomed EMA's plans to further improve the website's search functionalities and reminded EMA of the key importance of being able to understand what has changed when EMA updates its content, especially when it comes to guidance documents. They mentioned that industry users sometimes find content appearing in the wrong place or requiring update, as well as discovering updated content that they cannot see on the what's new page. In response, EMA explained that it stands ready to fix any such mistakes promptly and that it relies on users reporting these issues to be able to address them quickly.

Industry representatives welcomed EMA's plans to re-initiate the Key User Group where they will be able to discuss opportunities for improvement with EMA, mentioning areas such as the website's structure, functionalities and content management as examples.

Conclusion and follow-up actions

EMA is aware of the importance of its corporate website for key users, and is committed to making improvements to the website's content and functionalities that improve the experience of these users, taking their feedback into account. EMA and industry associations look forward to the planned re-initiation of the

[1] To help put this figure into context, an average website has only 7 pages and no documents.

EMA Website Key User Group, a forum for exchange of ideas, suggestions and proposals with the aim of continuously improving EMA's main communication tool.

Follow-up actions included the following:

- ☐ All users of EMA's corporate website are welcome to report any specific issues to newwebsite@ema.europa.eu at any time. Including as much information as possible enables EMA to address and fix issues promptly
- ☐ Industry representatives will send a list of issues and recommendations from their members to EMA at newwebsite@ema.europa.eu
- ☐ EMA will continue to work towards re-initiating its Website Key User Group within 2024
- ☐ EMA will continue to look into how to communicate changes made to its content clearly and consistently, including in its key guidance documents for industry stakeholders

7. Good manufacturing practice (GMP) inspections: how to ensure submission preparedness

EMA delivered a presentation concerning points to consider by applicants on assuring GMP preparedness for new marketing authorization applications. The presentation focused on key GMP information that applicants need to provide at pre-submission, submission (validation) of the MAA as well as during the procedure, to support with avoiding delays to validation and assessment procedure. Supply chain information at pre-submission stage can support early identification of GMP inspection and is encouraged, while noting that for accelerated assessments this is required in order to support the accelerated timetable. It was also emphasized that once the MAA has been submitted, the proposed manufacturing sites need to be inspection ready. While these are not new regulatory requirements, the points were emphasized in recent update (March 2024) of the EMA pre-submission guidance. See presentation.

Industry stakeholders delivered a presentation that highlighted areas where industry can improve on ensuring submission preparedness. It was highlighted that industry would appreciate if changes to guidelines are open for public comments, include an implementation date and are also delivered as track changes version (to allow identification of changes compared to previous versions). Industry welcomed the possibility of pre-submission interaction with EMA earlier on manufacturing and testing arrangements and are currently in the implementation phase for addressing the points raised in the pre-submission guidance. Industry stakeholders highlighted the areas that industry sees as further opportunities for improvement, including the inspection process and communication between regulators and with industry. Specifically on the release testing (Art. 51 of Directive 2001/83/EC requirements), industry recognises that it is a legal requirement. They question its relevance in some cases and would like to work with the European Commission for re-think of this concept.

It was noted in the follow-up discussion that consideration is necessary when defining batch testing waiver arrangements in the case of supply chains with sites located in different 3rd countries with which the EU holds Mutual Recognition Agreements (MRAs). It was emphasised that MRAs are bilateral agreements, and cannot have a combined interpretation. Special attention is necessary in the case of biotechnology products, where due to the complexity of its manufacturing process, the biological active substance is considered to be an integral part of the manufacturing process for the finished product. Applicants are encouraged to discuss such arrangements with EMA at pre-submission stage.

Conclusion and follow-up actions

Industry to continue implementing the EMA pre-authorisation procedural advice for users (updated March 2024) and is encouraged to reach out at pre-submission stage (via the EMA Product Lead) to discuss manufacturing and testing arrangements to ensure submission preparedness.

EMA to look into the proposed areas for improvement concerning and inspection and communication processes, and to continue engaging with industry via the dedicated interaction platforms.

8. Procedural aspects on the centralised procedure

EFPIA started with a presentation on the results of a survey to it affiliates on the centralised procedure that was followed by a joint presentation from industry associations on the progress on the focus group on submission predictability. Industry is fully committed to trying to help in addressing the ongoing issues with network sustainability. The survey provided some additional suggestions on how to improve the communication between EMA and applicants, in particular in relation to the 6-monthly emails regarding post-approval planned submissions.

EMA delivered a presentation outlining a number of ongoing initiatives across the Agency, many with industry participation, looking to ensure the sustainability of the network, improve submission predictability and shorten approval times. There was a specific deep-dive, into one such project: GIREX. This was a project initiated by CHMP members who were increasingly concerned with the lengthy clock-stops and multiple rounds of questions. The data confirmed that, compared to 2012, CHMP was granting a higher percentage of clock-stop extensions beyond the standards defined in their 2009 guideline. Multiple rounds of D180 List of Outstanding Issues were also noted. Based on this information, CHMP has agreed to revert back to a stricter implementation of the guideline and companies should be aware that there will be a much closer scrutiny on the requests for clock-stop extensions going forward. See presentation.

As part of the presentation, EMA also took the opportunity to inform industry that the use of the response template for initial MAA responses is now mandatory and to remind all stakeholders that there is a Multistakeholder Workshop on Submission Predictability planned for September 2024. *[Post-meeting note, date confirmed as 25 September]*.

Conclusion and follow-up actions

The Focus Group on Submission Predictability will continue to work and the close collaboration in trying to tackle the current pressure on the regulatory network is appreciated by all parties.