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Highlight report 11th Meeting of the industry stakeholder platform on the operation of the centralised procedure for human medicines

24 November 2023

Role	Name
Chair:	Alberto Gañán Jiménez
Present:	**Industry:** AESGP: Christelle Anquez-Traxler, Cottavoz Sylvie, Gisela Schaber, Kevin Turner, Klavdija Kmetic, Mihai Ionita. Alliance for Regenerative Medicine (ARM): Michael Werner. EFPIA: Fatima San Fourche, Laurent Desqueper, Lynsey Flitton, Mireille Muller, Pär Tellner*, Rebecca Lumsden, Simon Bennett*, Stefan Schwoch*, Susan Bhatti*. EUCOPE: Axel Korth, Joao Duarte, Laura Liebers, Marcello Milano, Maren von Fritschen*, Mariska Mulder*, Nasir Hussain, Roberta Bernadelli, Teresa Pepper. EUROPABIO: Almath Spooner*, Marcello Milano, Pedro Franco*, Valentin Plouchard*. EUROPHARM: Alain Verrijdt. MEDICINES FOR EUROPE: Alexander Gehrke*, Beata Stepniewska*, Britt Vermeij*, Caroline Kleinjan*, Hanjoon Kim, Lázár Balázs, Lioara Bota, Mireia Roig, Nivedita Roy, Preeta Mathur, Sophie Dagens. MPP Association: Barbara Gollob, Fanny Barbotin, Fatima Bennai-Sanfourche, Juan Carriquiry, Mateja Ravnikar, Samuel Gavillet, Shayesteh Fürst-Ladani. VACCINES FOR EUROPE: Agnes Legathe, Alexandra Oger, Anna Czwarno*, Helena Ardebrant, Monica Perea Velez, Stephane Callewaert, Susanne Heiland-Kunath, Tiago Fonseca*. **EMA:** Alberto Gañán Jiménez*, Alex Barbosa Correia, Alexios Skarlatos, Alexis Nolte, Brendan Cuddy, Corinne de Vries, Christelle Bouygues, Eftychia-Eirini Psarelli, Elsie Merken*, Enrico Tognana, Fabrizio Bocassi, Francesca Day*, Francisco Penaranda*, Isabel Chicharro, Kristiina Puusaari*, Marcos Fernandez Gomez, Marie-Helene Pinheiro, Maria Filancia, Marine Bunch*, Mark Fahmy*, Radhouane Cherif, Rosa Gonzalez-Quevedo, Sandra Vanlievandel, Sara Pulido Sanchez*, Silvy da Rocha Dias*, Sonia Ribeiro, Thomas Girard*, Virginia Rojo Guerra*. **EMA scientific committees and working parties:** Harald Enzmann **European Commission:** Kaili Semm

* In person attendance

This report summarises the 11th 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.

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1. Revised Variation Framework

The EC presented the revision of EU variations framework for medicines of human use. A first step to review the variation Regulation and the variations guidelines, independent to the revision of the new EU pharmaceutical legislation and a second step after the EU pharmaceutical legislation review. See presentation here.

EC informed Industry representatives that the draft delegated act on variations will be released for public consultation early 2024. Industry will have 4 weeks for providing comments. The variations classification guidelines will be reviewed in parallel. Industry associations will be informed on exact timelines.

The review aims to further optimise EU variation process efficiency including simplification of grouping requirements and worksharing procedures and to provide more flexibility to regular updates of the variation guidelines.

It was highlighted that on the first step, the framework for biological medicinal products will be updated and additional scopes for medical devices will be added. The review will also add new scopes related to vaccine updates and references to veterinary medicinal products will be removed.

Industry stakeholders welcome the revision of the EU Variation Regulation and classification guideline that will modernise and simplify the framework. For the regular update of variation guidelines, Industry suggested to the EC to consider a possible delegation of the classification guidelines to EMA/HMA. Industry recommends the downgrading of classification of changes for biologics in line with small molecules, the reduction of the burden on IA/IAIN and changes towards implementing of ICH Q12 principles.

Conclusion and follow-up actions:

The EU draft delegated act on the new Variation Regulation will be released of public consultation early 2024. Industry will have 4 weeks for providing comments. The variations classification guidelines will be reviewed in parallel.

2. Updates on digitalisation: eAF for variations and implementation of IRIS for variations 61.3 and MAH transfers and next steps

EMA presented both projects 'PLM Portal web based eAF' (currently available for Centrally Authorised medicinal Products (CAPs) variations) and IRIS Regulatory Procedure Management (RPM) for variations, Article 61.3 and Marketing Authorisation (MA) transfers. In addition, a clarification on the different EMA portals and products contained under the Value Stream PLM (Product Lifecycle Management) was presented. See presentation here.

EMA made a presentation on the expected timelines for IRIS RPM and the level of communication and engagement with Industry. Subject to successful User Acceptance Test (UAT) performed in November 2023, the intention is to go-live in 1Q 2024 with a subset of selected generic medicinal products. Industry Subject Matter Experts (SME) from 7 industry (trade) organisations representing from both Human and Veterinary pharmaceutical industry are involved in variations, Article 61.3 and MA transfers process development and onboarding in 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.

In parallel, the EMA will continue implementing other post-authorisation procedures in IRIS during 2024. The work has started recently with PSURs/PAMs. The same level of engagement with Industry SMEs is expected. EMA gave an overview of the upcoming key activities for the web based eAF and explained the key dependencies and enablers that must be fulfilled prior to expanding the use of the forms for nationally

authorised products. The team will give an update on the next key deliverables following an Agile planning event in December 2023.

Industry presented the results of a recent survey on the use of Web eAF for CAPs. Results showed a limited use of eAF by MAHs of CAPs after its launch. Based on the results, Industry provided some recommendations for consideration in the extension of eAF for variations to nationally authorised procedures (NAPs) including an improvement of the system performance and highlighted the need to ensure data quality for NAPs. Industry also pointed out the need for enhanced support on change management taking into account the larger pool of MAHs dealing with MRP/DCP and national regulatory procedures.

Conclusion and follow-up actions:

It was recognised a good level of engagement with Industry and encouraged to maintain it in the future for new implementations. It was also recommended to inform MAHs with the necessary time for any new product to be onboarded in IRIS for variations, Article 61.3 and MA transfers.

3. Patient engagement in centralised procedure: from a patient centric drug development to authorisation

The Agency provided an update on the ongoing work on Patient Experience Data (PED) and progress since the last discussion in June 2023. The Agency presented a draft action plan where all actions on PED are being consolidated to ensure coordination, resource efficiency and oversight. Two of the actions, which are reflected in the EMANS' delivery plan and CHMP's 2023 workplan, remain key priorities: a Reflection paper on the best EU approach to generate, collect and analyse PED, and to explore how to improve transparency in the AR. See presentation here.

Since last summer, EMA has started to pooling cross-Agency expertise on PED and has also set up a group of experts from the Network to consolidate all multi-disciplinary expertise on PED across the EU. This group will be in charge of drafting the reflection paper on PED. Experts have been identified from CHMP, PRAC, PDCO, CAT, COMP, Methodology WP, Oncology WP, Scientific Advice WP and Big Data Steering Group.

The Agency also used this opportunity to clarify that the timelines for the 1st draft have been slightly adapted and the public consultation is now expected in 2Q 2024. EMA took the opportunity to clarify that the scope of the reflection paper will differ from the planned ICH guidance and will not cover specific methodological guidance, but rather will provide a framework for developers on the EU approach to PED.

Conclusion and follow-up actions:

EMA will start drafting the reflection paper with the experts from the Network and in parallel will discuss how to further improve transparency in the assessment report. Further updates will be provided to industry and other stakeholders as work progresses.

4. Working parties and new ways of working

EMA presented an update on the implementation of the new operational model for the working parties (WPs). This update included changes to stakeholder engagement and the new EU survey tool to capture comments on guidelines. See presentation here.

The working parties have been regrouped into 5 different domains: quality, non-clinical, methodology, clinical and veterinary. The new target operational model for the WPs includes a domain governance which has the oversight over the European Specialised Expert Communities and coordinates the strategic activities

related European Medicines Agencies Regulatory Network (EMRN) /Regulatory Science Strategy (RSS) as well as stakeholder engagement in relation to the workplans of the working parties.

An overview of the re-organisation of the quality domain during 2023 was presented, which included the Quality Working Party, Biologics Working Party and the Biosimilar Medicinal Product Working Party. The Quality domain prioritised expertise in the reorganisation, taking into account the geographical spread of the nominations.

For the stakeholder engagement, it is now foreseen at two levels: 1) at the level of the domain governance, which would be on the workplans, 2) at the level of the WP, for discussion on specific scientific issues with interested parties or webinars on new/revised guidelines, as foreseen in the 3-year rolling plan.

In line with the European Medicines Agencies Network Strategy to modernise processes and to create a supporting digital infrastructure as part of the goal of the digital transformation at the Agency, a new EU survey has been implemented for the collection of comments of draft guidelines during public consultation. This new tool is designed to facilitate the submission and collection of comments in a more flexible way.

Conclusion and follow-up actions:

There has been the successful implementation of the re-organisation of the working parties from the Quality domain in 2023, following the reorganisation of the Non-clinical, Methodology and Clinical domains in 2022. With the new model, there is a structured stakeholder engagement with specific aims at the domain and WP level. There is now a new digital tool in the form of an EU survey that will be used for collection of comments and is now rolled out for all public consultations on guidelines and workplans at the Agency.

5. Update on the Submission Predictability Focus Group

EMA presented the latest data for the MAA monitoring exercise which has taken place during 2023. See presentation here.

Despite the re-baselining in June 2023, the data clearly indicate that on average less than half the MAAs with Letter of Intent (LoI) come on the date which was indicated on the pre-submission form. Given that the monitoring exercise has not yielded any changes in behaviour, EMA has decided to introduce more active measures. The first such measure, presented in detail at the meeting, is the introduction of an annex to the LoI form. This annex serves 3 main purposes:

- Clearly expresses the LoI and Rapporteur appointment as "booking an appointment", and consequently resources, with EMA and 3 NCAs (Rapporteur, Co-Rapporteur & PRAC Rapporteur) and therefore the importance of accurate information.
- Will allow more context around the declared submission date.
- Gives Member States more details on submissions, so they can make better informed bids.

The new annex will become effective from January 2024.

The EMA also took the opportunity to inform stakeholders of a planned clean-up of the SIAMED database. There currently are around 300 products with a latest-known submission date of 2021 or earlier. About 60 of these products have Rapporteurs appointed. Given the time expired and the lack of information on submission intentions, these products will be deleted from the database, meaning that a new Eligibility request will have to be submitted.

EMA will email all the Applicant contacts for these 300 products ahead of the planned clean-up, so that they will have the opportunity to submit a new intended submission date if relevant. It is therefore vital that all Applicants keep their contact information with EMA up to date.

A joint presentation from Industry Associations agreed with the conclusions on submission predictability and made a few proposals on other potential measures to be discussed at the forthcoming Focus Group meeting in January 2024.

Conclusion and follow-up actions:

It was agreed that discussions would continue in the dedicated Focus Group on Submission Predictability and outcomes and any other future measures will be reported in upcoming platform meetings.

Post meeting note: The Annex to the Letter of Intent was published in December 2023 and can be found in the following link.

6. Windsor protocol implementation aspects

EMA presented an overview on the recent developments on the Protocol on Ireland / Northern Ireland (the 'Protocol')/Windsor Framework and the main implications of Regulation (EU) 2023/1182 for centrally authorised medicinal products for human use aiming to address the practical challenges faced by citizens and businesses in Northern Ireland with the operation of the Protocol and to protect the EU's single market. See presentation here.

In particular, it was highlighted that medicinal products for human use that are eligible for the centralised procedure will be placed on the market in Northern Ireland in accordance with the law of the United Kingdom and under the terms of the authorisation granted by them as of the date on which Regulation (EU) 2023/1182 becomes applicable.

Additionally, it was noted that MAHs should prepare to adapt the product information of CAPs by removing the reference to the local representative in Northern Ireland in the package leaflet and/or to update the labelling aspects where multi-county packs including Northern Ireland/UK and an EU/EEA member state are in place, where applicable. Further references were made on the fact that parallel distribution with Northern Ireland will cease to be possible for human CAPs, on the transitional provisions lay down in this Regulation for medical products lawfully placed on the market before the date it becomes applicable and the entry into force and application of this Regulation. The Industry Stakeholder were reminded to prepare on any regulatory, labelling and/or supply changes required for the implementation of Regulation (EU) 2023/1182 to ensure compliance with the Protocol and the continuous supply of medicinal product.

Industry shared their considerations on the impact of Regulation (EU) 2023/1182 that expected for the markets of Ireland and United Kingdom, the regulatory impact on the marketing authorisations, the industry ongoing preparation, challenges and expectations. Industry asked for clear regulatory guidance and clarification of the timing for entering into force.

Conclusion and follow-up actions

EMA will publish guidance on the impact of Regulation (EU) 2023/1182 for centrally authorised medicinal products for human use at the beginning of January 2024.

Industry should inform on additional challenges and/or concerns that they expect to encounter and to discuss forthwith with the relevant Authority any expected supply disruptions in particular for small markets historically dependent from the UK.

Post meeting note. The EMA guidance was published on 5 January 2024. See 'Questions and answers to Stakeholders on the implications of Regulation (EU) 2023/1182 for centrally authorised medicinal products for human use' here. EMA will send a direct communication to contact points of CAPs during January 2024.

7. Update on Issues Raised During Validation of Type IB and Type II Variations

EMA presented an overview of common validation issues identified for type IB and type II (non-clinical, clinical and RMP) variations. The presentation also covered the available guidance and tools to assist applicants in preparing variation submissions. The use of these resources, such as the validation checklists, the published guidance/Q&A or the query box/email, can help minimizing the number of requests for supplementary information during validation. See presentation here.

Industry representatives welcomed the presentation, in line with their experience, and the EMA's efforts to minimise validation issues. Suggestion was made to consider including additional validation checks during the technical eCTD validation (e.g. check for missing documents or missing signatures) to potentially help reduce the number of validation issues. Industry representatives also indicated it is anticipated that introduction of eAF PLM could help reduce frequently occurring administration issues.

Conclusion and follow-up actions:

The feedback collected will serve to identify any area where guidance would require update.

8. New in 2024: Opportunity to submit Standard for the Exchange of Non-clinical Data (SEND) data packages in centralised procedures

From January 2024, EMA is launching a proof-of-concept study to evaluate the added value of using SEND data in the evaluation of new Marketing Authorisation Applications. Applicants are encouraged to submit their SEND data packages, in addition to the eCTD format, as part of their MAA submission. Detailed instructions will be made available on the e-submission website. See presentation here.

SEND is the Standard for Exchange of Nonclinical Data between organisations, which provides a standardised format for the submission of nonclinical data to regulatory bodies. SEND was created by the Clinical Data Interchange Standards Consortium (CDISC) in 2002 to execute on the Study Data Tabulation Model (SDTM) for the submission of non-clinical studies. A SEND dataset package contains the SEND datasets (.xpt files), the Nonclinical Study Data Reviewer's Guide (nsdrg.pdf), and the Define XML Document (define.xml).

Standardisation of data presentation has been shown to considerably reduce the time regulators require for reviewing the non-clinical data packages. In this proof-of-concept study, we will evaluate whether using SEND data in the assessment of the non-clinical dossier will lead to improved and more consistent quality of assessments, to more science-driven questions to applicants, and to faster completion of the non-clinical dossier assessment.

Conclusion and follow-up actions:

This process will go live in early 2024. The findings on process (i.e. not on confidential information) will be made public. A progress report plus a discussion with industry stakeholders on their experience with this study is foreseen for the next centralised platform meeting.