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Human Division

# Highlights from the 18th EMA Industry Platform meeting on the operation of EU pharmacovigilance legislation – 22 November 2023

The following records announcements and action points from the 18th Pharmacovigilance Industry Platform meeting.

## Welcome and matters arising

- E. Korakianiti and S. Straus welcomed the participants to the EMA Industry Platform.

## Artificial Intelligence in Pharmacovigilance

- EMA updated on their approach to AI, with three key drivers to the digital transformation at the Agency: process analytics, regulatory submissions, and healthcare data analytics. The Agency is building external collaborations in the areas of legislation and guidance development, with specific collaborations on AI in pharmacovigilance including in the CIOMS group or at the FDA. Pharmacovigilance, including signal detection, is an interesting topic for AI, as AI can help scale processes, although the need for a human-in-the-loop remains. EMA presented several practical pharmacovigilance AI use cases they have analysed. Finally, EMA highlighted the importance of dialogue with industry and reminded industry stakeholders that they can engage through the public consultation on the Agency's reflection paper.

  https://www.ema.europa.eu/en/documents/presentation/presentation-update-ai-pharmacovigilance-ema-j-durand-ema_en.pdf

- EUCOPE, on behalf of industry stakeholders, elaborated that while AI use for case processing and causality assessment has been already in place in larger organisations, challenges remain for small population or rare indications. The focus at present is on a qualitative review, with significant costs of developing AI models.

- **Action:**

  Industry stakeholders to comment on the draft reflection paper on the use of artificial intelligence in the lifecycle of medicines until the end of 2023.

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## Good Pharmacovigilance Practices (EU-GVP) - Update

- The regulators updated on the work related to the guidelines, with rev. 3 of GVP XVI and its Addendum on RMM effectiveness evaluation close to finalisation (to be published end Q1/beginning Q2 2024). Industry stakeholders' comments sent during the public consultation were acknowledged. The work on GVP Module XVI Addendum III on pregnancy prevention programmes and GVP Chapter P III on pregnancy and breastfeeding continues as both are aimed to be published within 2024 or Q1 2025 (the Addendum). Reflecting on the two multistakeholder meetings and written contributions, the Reflection Paper on digital support to RMM and their evaluation shall be published in 2025. Finally, the consultation phase for the GVP Module VIII rev. 4 on post-authorisation safety studies will be launched in March/April 2024 to consider among others, feasibility assessment, the implementation of ICH-M14, definitions of Regulation (EU) No 536/2014). While a revision of GVP Module V on risk management system is planned, there is no consultation timetable yet.

  https://www.ema.europa.eu/en/documents/presentation/presentation-update-good-pharmacovigilance-practices-eu-gvp-p-bahri-ema_en.pdf

- The industry welcomed the feedback received and sought to clarify if any work related to the revision of the off-label use, or revision of GVP IX regarding generic products has been undertaken. Additionally, a question was received related to environmental risk assessment (ERA) in the context of the revision of the EU pharmaceutical legislation. The regulators welcomed all feedback on the guideline development (see Action). As regards ERA, since the Agency is not in charge of the legislative proposal, EMA referred to the EC for further clarification.

- **Action**: Industry Stakeholders to share with the regulators their use case on generic products as well as their question on the off-label use to be considered for the next revisions of relevant guidance documents.

## Risk Management Plans (RMPs): transparency and follow-up questionnaires

- The regulators clarified that all RMPs in all procedures with outcome on or after 20 October 2023 (iMAA Opinions, variations CHMP Opinions, IB notifications, PRAC recommendations, etc.) will be published on the EPAR website of a respective product. The documents to be published will be redacted with the MAH and EMA agreeing on the final document. The regulators have provided a reference to an updated guidance, which aims to clarify pre- and post-authorisation procedural aspects, link here. Overall, the EMA evaluation after the first RMP checks is encouraging, and this will feed into the re-evaluation of the process and MAH requirements early next year, with the view to simplify the interactions. The regulators clarified that as now the full RMPs are published, the utility of the summary of the RMP will be considered at the revision of the GVP V and RMP templates, in close collaboration with the Commission.
- The regulators presented the draft text of the Guideline on Specific Adverse Reaction Follow-up questionnaires (Specific AR FUQ) for which the public consultation will start shortly. The Guideline offers a comprehensive guidance to the EU regulatory network regarding the appropriate utilization of the Specific AR FUQs in routine pharmacovigilance. The completeness of information within Individual Case Safety Reports (ICSRs) is critical for effective assessments. Frequently, these reports lack essential data necessary for a thorough understanding of reported adverse reactions.

To address this limitation, various forms, and questionnaires, including general FUQs and Specific AR FUQs, are commonly employed to collect additional information. This guidance primarily focuses on Specific AR FUQs developed by MAHs at the request of NCAs. It does not seek to modify MAHs' internal policies for FUQs but rather emphasizes the importance of obtaining structured and detailed information on adverse reactions that may impact a product's benefit-risk balance or have implications for public health. The document outlines three key areas: general guidance on when and how to use Specific AR FUQs, guidance for creating them, and considerations for their discontinuation and removal. Specific AR FUQ should be employed for safety concerns that could affect a product's benefit-risk balance. The development of this guideline and especially the proposal for a publicly available repository of the Specific Adverse Reaction Follow-up questionnaires was welcomed by the industry.

https://www.ema.europa.eu/en/documents/presentation/presentation-rmp-publication-and-specific-adverse-reaction-follow-questionnaires-guideline-e-cochino-ema_en.pdf

- **Action:** The start of public consultation of the guideline was announced for 6 December 2023 and will be open for nine (9) weeks.

## PASS update

- Following on last year's meeting, the regulators announced the upcoming catalogues that will replace the current ENCePP Resources Database and the EU PAS Register at the beginning of 2024, offering an improved, more efficient service for researchers, regulators, and pharmaceutical companies. These catalogues will help users identify suitable studies and data sources to address research questions related to the use, safety, and effectiveness of medicines through a set of collected metadata (data elements characterising both data sources and studies). Also, the catalogues will provide helpful information to facilitate the conduct and interpretation of studies. Users will benefit from a modern technology with enhanced view, search, export, and data submission functionalities. The catalogues aim to promote transparency, build trust in observational research, and encourage the use of good practices.
- The regulators have also updated on the activities currently ongoing on the post-authorisation safety studies, including the EU Clinical Trial Regulation, the need of alignment with new/updated guidelines (e.g., EMA guideline on registry-based studies) and international standards (e.g., HARPER), to need to adopt definitions, implement changes related to the experience of PASS assessors, and to amend related templates.

  https://www.ema.europa.eu/en/documents/presentation/presentation-ema-hma-catalogue-non-interventional-studies-eu-pas-register-new-functionality-cochino-ema_en.pdf

  https://www.ema.europa.eu/en/documents/presentation/presentation-gvp-module-viii-post-authorisation-safety-studies-c-jonker-ema_en.pdf

- **Actions:**

  1. EMA to announce a 2–3-week downtime in the current system shortly before the opening of the functionalities.

  2. The regulators to launch the public consultation of the GVP Module VIII - Post-authorisation safety studies beginning of 2024.

## EudraVigilance update

- EFPIA, on behalf of Industry stakeholders, presented the topic of ICSR replication issues on EudraVigilance and within MAH PhV system creating problems in data retrieval, cleaning, and analysis. While duplicates are created when one ICSR with many AEs and co-suspect medicines leads to the creation of multiple duplicates, the replication occurs with contractual partners, resulting in further submissions to competent authorities worldwide due to multiple partnerships. The issue has been already published (doi: 10.1007/s40264-022-01251-7), it affects all spontaneous reporting systems, from MAHs to regulators and health bodies, and some estimate as between 0.5 – 2% of database being populated with replicated ICSRs. The industry stakeholders noted this as a hurdle to signal detection and highlighted the lack of a uniform way of tackle the issues. Upon reflecting, several stakeholders voiced similar concerns, from the generic perspective, rare disease area, innovator industry and the regulators and all agreed that more legislative solutions are needed. The regulators commented that the problem has been already described and they are working with other regulators to try and find a coordinated way to alleviate the problem.
- **Action**: EMA to liaise with the EC and other regulatory agencies to tackle the problem of ICSRs' duplication and replication.
- EudraVigilance now contains more than 28 million ICSRs referring to 15,7 million individual cases. Following on last year's meeting, when industry stakeholders were notified about an issue where case narratives from EudraVigilance were accessed and downloaded by certain MAHs and transferred in full, without further redaction of personal data, to third countries, EU regulators have reminded that the EudraVigilance system must remain a trusted system by patients and healthcare professionals. This requires that all stakeholders involved in the processing of health data within EudraVigilance (including access/download) comply with the applicable data protection rules (General Data Protection Regulation (EU) 2016/679) and apply appropriate safeguards where an international transfer of personal data occurs. Earlier this year, the European Data Protection Supervisor (EDPS) conducted an audit of EudraVigilance and related processing activities considering the different roles and responsibilities of stakeholders involved. EMA is awaiting the audit report which will further inform if further enhancements will be required.
- The regulators highlighted an initiative of compliance checks to be sent to MAHs, NCAs and commercial and non-commercial sponsor of clinical trials registered in EudraVigilance. These compliance reports are intended to support the legislative requirements on collaboration between the EMA, NCAs and MAHs and to ensure EV data quality and adherence to the timelines. In the preparation step, until March 2024, a pilot including stakeholders from the EV-EWG is being undertaken. Once the feedback is analysed and implemented, the compliance checks will be initiated. Further communications and engagement with industry stakeholders and inspectors are foreseen to ensure an adequate implementation with an aim of an automatic generation from the EVDAS system, i.e., from its clinical trials and post-marketing modules.
- Finally, the regulators referred to a longer-term project, Signal & Safety Analytics (SSA) vision, to replace the technology behind EVDAS, the reaction monitoring report (eRMR), and adrreports.eu website, aiming at improved performance, enhanced user interface, and implementing a more user-oriented approach of retrieving data from EV. The EVDAS has been in place for years and some performance issues emerged as well as the lack of flexibility in querying the data. This became apparent during the COVID-19 pandemic, with high demand from the public to have more tools to retrieve the data from the current adrreports.eu website. All current stakeholders (EMA, NCAs, MAHs, the public) will be affected by the change at a different pace. The initial scope (1st

phase) will cover the core functionalities for signal detection and validation for EMA and NCAs, no changes to be expected for MAHs in 2023 and 2024. The MAHs had already the possibility to engage in the project via the EudraVigilance Expert Working Group, this will be continued.

## Conclusions and next steps

Regulators and Industry stakeholders acknowledge the benefit and importance of continued dialogue noting the progress achieved since the pharmacovigilance platforms were set up initially to support pharmacovigilance regulation implementation.