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Human Division

Highlights from the 19th EMA Industry Platform meeting on the operation of EU pharmacovigilance legislation – 15 November 2024

The following records announcements and action points from the 19th Pharmacovigilance Industry Platform meeting.

Welcome and matters arising

- E. Korakianiti welcomed the participants to the EMA Industry Platform, including PRAC and CMDh members, EMA and all industry associations.

DARWIN EU and RWE studies in medicines regulation

- The regulators summarised how DARWIN EU is used in regulatory decision making on medicines by enabling the use of real-world evidence (RWE) studies. They presented various use cases across the medicinal product life cycle focusing on pharmacovigilance (PV) procedures. Thanks to a federated network of centres, and the use of a common data model, consistency in analysis can be achieved. Overall engagement with industry stakeholders is facilitated through the DARWIN EU advisory board, while study specific engagement with innovators is envisaged for complex studies. For such the innovator will receive the final version of the protocol for a 10-day consultation. Finally, the regulators presented the overview of studies conducted by the network so far, which can be accessed here:

  www.ema.europa.eu/en/documents/presentation/presentation-darwin-eu-how-rwe-transforming-regulatory-decision-making-segec_en.pdf

- Industry stakeholders sought to clarify which topics qualify as a DARWIN EU study and which criteria are met for complex studies. Regulators clarified that complex studies cannot be answered readily by existing analytical packages or require complex work on the code or (outcomes) phenotyping. They emphasised that all topics where there is a need for further analysis of RWE, and for which eligible data can be identified, could qualify for DARWIN EU study, while for some rare and often drug-induced outcomes, e.g., adverse drug reactions including severe cutaneous adverse reactions, the review of the spontaneous case reports from data bases may provide sufficient evidence for a causal association.

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PSUR updates

- The regulators updated on the new approach following the removal of Section 6 "Other considerations" from the PSUSA AR in relation to extrapolation of PSUSA outcomes from mono-components to fixed dose combinations or vice-versa, as well as for drug-drug interactions when the interacting product is a NAP. The changes stem from a pilot initiated by PRAC where CMDh provided its input. The extrapolation of the PSUSA outcome to a CAP will be communicated to the concerned MAH via EMA, based on evidence reviewed in the PSUSA for a CAP/mixed CAP/NAPs or NAPs and endorsement by PRAC, while the extrapolation to NAPs will be included in the published CMDh meeting minutes. Accordingly, CMDh Q&A on Pharmacovigilance legislation number 10 has been updated to reflect the new agreed approach. All PSUSA report templates were updated in accordance to reflect the new approach. The regulators reminded industry stakeholders to keep their product information up to date with the scientific knowledge and submit relevant variations at national level also in case no information is included in the CMDh minutes. Finally, two real-procedure examples were presented, namely dydrogesterone / estradiol and estradiol-nomegestrol.

  www.ema.europa.eu/en/documents/presentation/presentation-agreed-approach-post-section-6-pilot-psusa-m-escudeiro-dos-santos-b-pelle_en.pdf

- As a follow up to the 17th EMA industry meeting, EMA on behalf of the PRAC Granularity and Periodicity Advisory Group (GPAG), informed that the work concerning the assignment of PSUR frequencies and data lock points (DLPs) dates for about 1,000 entries for which PSUR assessments were initially deferred since the PSUR assessment of other active substances was prioritised at the time of the EURD list creation, has been completed. The statistical tool developed for this purpose is further described here. The implementation of the new PSUR frequencies and DLPs in the EURD list has been conducted in different phases since 2023 and will be finalised in the next EURD list update. Marketing authorisation holders (MAHs) were reminded that they can propose and justify a new PSUR frequency with their upcoming submission for Lead Member States assessment. Concerning reporting periods for the first PSUR submitted at EU level, industry associations were reminded of the following: 1. if a substance has never been assessed in a PSUR in EU, the first PSUR submission should include all relevant data since launch until the DLP date as published in the EURD list, 2. if, however, a PSUR has been previously submitted in EU (e.g., at a national level), the reporting period should cover from the DLP of that PSUR until the DLP stated in the EURD list. It's acknowledged that the reporting period for the first PSUR will cover a longer period than the one indicated by the PSUR frequency in the EURD list. All MAHs are reminded to check the EURD list and consult the frequency of submission, as it is updated regularly.

- Industry stakeholders commented that the impact of this completed work on industry workload has been large and highlighted the importance of keeping the "notes" field populated by the regulators. It has been clarified that the only change no longer included in the 'notes' field are the changes related to the Lead Member State. Any other clarification is welcome in the EURD mailbox (EURDList@ema.europa.eu). Industry inquired also whether the changes to the frequency for these substances would reflect the need of regularly updating the product information (PI) for generics. The industry association was reminded that MAHs have the responsibility to be aware of safety updates for their product, including for the generic medicinal products, which should follow the innovator's changes to PI.

  www.ema.europa.eu/en/documents/presentation/presentation-agency-european-union-psur-frequencies-active-substances-dlp-2025-based-risk-based-approach-m-lopez-fauqued_en.pdf

Non-fixed Drug Combinations & Pharmacovigilance

- EFPIA introduced a topic of non-fixed drug combinations encompassing in EFPIA's experience mainly medicinal products used in oncology area. They emphasized that unlike for a fixed drug combinations, guidance is not readily available in the respective areas of licence, labelling, expedited & aggregate reporting, risk management planning and safety surveillance, as well as to which regulatory authorities to report. They questioned the practical approaches to signal detection for both the combination and the mono-component. Finally, EFPIA proposed to develop some additional guidance principles, either in a dedicated Q&A or in a few closely related GVP modules (V, VI, VII and IX).
- The regulators emphasised that as labelling and safety were concerned, the presentation of ADR information should be based on the determination and assessment of a possible causal association which is then presented in Section 4.8 as specified in the EC Guideline on SmPC. The sources of this information include clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports. Adverse events without at least a reasonable possibility for being causally related to the medicinal product should not be listed in the SmPC.
- Regulators intervened that while there is clear EU guidance that all reports of suspected adverse reactions should be transmitted to EudraVigilance, there is no definition of 'non-fixed drug combination'. They sought clarification on what EFPIA would consider within the scope if this term, e.g., which treatment protocols and medicinal products. Industry highlighted that there is a section on multi-drug regimens in GVP Module VII on PSURs.

  Post-meeting notes:

  1. This guidance in GVP Module VII refers to active substances authorised as a component of a multi-drug regimen. For example, a product may be authorised as an add-on therapy. According to this guidance in GVP, the MAH should include a summary of important safety findings from use of the active substance in combination therapy in the PSUR.
  2. Industry associations are advised that the existing *Guideline on the clinical evaluation of anticancer medicinal products* adopted by CHMP in Nov 2023 provides guiding principles for several treatment regimens, safety considerations including basic and extended concepts, safety databases and reporting in special population as well as presentation of oncology ADRs in product information.

  Actions:

  1. Industry stakeholders to share any suggestions for the RMP template to facilitate this group of products.

  2. Industry stakeholders to consider using a real product (under iMAA or in post-approval phase) submission to pilot an RMP with modified content to address the challenges industry associations may be facing. EMA product team would provide support pre-submission, together with GVP V coordination team.

Guidance update

- The regulators updated on the ongoing revision of the *Guideline on Risk assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling,* initially adopted in 2008 and part of both CHMP and PRAC current working plans. Public consultation has been completed with industry association providing their comments. Publication expected in 2025.

  www.ema.europa.eu/en/documents/presentation/presentation-revision-guideline-risk-assessment-medicinal-products-human-reproduction-lactation-data-labelling-d-duarte_en.pdf

- The regulators updated on the completed Module of GVP XVI Rev 3 on risk minimisation measures (RMM) and Addendum II on RMM evaluation and well as the definitions GVP Annex I Rev, on the ongoing revisions of GVP Module XVI Addendum I on proactive risk minimisation for teratogenic medicines in non-pregnant persons, GVP Chapter P III on pregnancy and breastfeeding as well as the Reflection Paper on digital support to RMM and their evaluation. Further prioritisation work will focus on modules on post-authorisation safety studies, risk management systems and vaccines, the latter to incorporate knowledge gathered during the ten years of its applicability and on pharmacovigilance operations and methods for COVID-19 vaccines. Other modules will be revised after the publication of the amended Implementing Regulation (IR) (expected in 2025).

  www.ema.europa.eu/en/documents/presentation/presentation-update-good-pharmacovigilance-practices-eu-gvp-p-bahri_en.pdf

- The industry stakeholders welcomed the update and sought to clarify if any work related to the revision of the GVP IX regarding the update of IR could serve also as an opportunity to introduce additional suggestions on the signal detection for generic vs. the innovative products.

  Action: Industry stakeholders to share their use case on generic products to be considered for the next revision opportunity of GVP IX.

AI in pharmacovigilance – EMA update

- EMA updated on the European medicines regulatory network (EMRN) 2023-2028 AI work plan, encompassing guidance, policy and product support, tools & technologies as well as experimentation, collaboration and change management. Experimentation on the use of AI in PV at the Agency has so far focused on the handling of ICSRs originating from the medical literature to reduce duplication in EudraVigilance, on the semi-automated screening of literature abstracts to support signal detection, on the extraction of ADRs listed in SmPCs and their integration in signal management workflows, on the automated adjudication of case reports to support signal review, as well as on signal prioritisation based on historical data. They presented various groups dealing with methods innovation, including SMART Methods, Digital Transformation and Data and Methods taskforces at the EMA, as well as collaborations focussing on AI in PV, namely CIOMS Working Group XIV and AI in PV clusters with FDA. The draft report *CIOMS Working Group XIV* should be released for a 6 weeks' public consultation in spring 2025.

- Industry stakeholders welcomed the plans to make the "listedness" database public to replace the PROTECT database of adverse drug reactions (EU SPC ADR database), which is pending a manual check of a small percentage of unstructured information not captured by the large language model (LLM). They have also expressed interest in targeted AI tool for automated detection of signals or in the field of ICSRs "Deduplication".

  www.ema.europa.eu/en/documents/presentation/presentation-agency-european-union-ai-pharmacovigilance-ema-update-j-durand-l-pinheiro_en.pdf

Action: Industry stakeholders to comment on the draft report of *CIOMS Working Group XIV* when released for public consultation.

EudraVigilance update

- EMA in collaboration with the NCAs in the Member States and the EudraVigilance Expert Working Group, is developing a masking policy for the personal data held in the EudraVigilance database. This action has been triggered by the 2023 European Data Protection Supervisor EV audit, and their recommendation to develop a common masking policy which should be complied with all EV reporting entities. Following a risk assessment, a proposal was made for 14 E2B data elements relating mainly to the reporter's and patient's details to be masked using a null flavour, while 12 E2B data elements relating to sender's details to be left blank for the submission to EudraVigilance. Industry associations were assured that from EMA's perspective the proposed level of masking will not compromise duplicate detection activities. It is expected that the policy will be finalised and adopted during 2025.

  www.ema.europa.eu/en/documents/presentation/presentation-eudravigilance-masking-policy-personal-data-r-postigo_en.pdf

- European Conference of Pharmaceutical Entrepreneurs (EUCOPE), representing small and mid-size companies, updated on the importance of the quality of the case follow up, defined as a complete and accurate set of E2B fields to assure medical cohesiveness in data interpretation for proper causality assessment. The example approaches of follow-up (FU) including phone call or written follow ups were presented. Response rates varied from 26% for phone call to as little as < 2% for email in one global partner company. Further on industry described response rates per specific case category (e.g., innovative product vs. generic, case causality) in a peer-reviewed publication. EUCOPE proposed a risk-based approaches to case FU by enhancing HCPs education incl. support and training, providing clear reporting guidelines, and by leveraging technological advancements. Finally, EUCOPE, jointly with EFPIA, suggested to explore ways for increasing responses success rate via pragmatic FU collections.

- The regulators acknowledged the challenges described and signalled that a PRAC *Guideline on Specific Adverse Reaction Follow-up questionnaires* (Specific AR FUQ) shortly to be published may tackle some challenges presented.

- As a follow up to 18th EMA industry meeting, Medicines for Europe (MfE), presented their proposal to reduce replication of ICSRs. Their proposal offers a proactive prevention of the creation of duplicates by targeted legislative changes for off patent medicinal products, as well as relying on the WHO database, Vigibase, as a reference for signal detection. MfE clarified that this proposal has been included in their Position Paper on Pharmacovigilance Agreements published in Aug 2022.

- The regulators acknowledged this proposal and followed up with the progress in the de-duplication work at EMA including enhanced tools and updated on the legislative work currently ongoing at the EC.

  Actions:

  1. Industry stakeholders to engage with EC for their legislative proposal regarding the proposed solution on the issue with duplicates.

  2. Industry stakeholders encouraged to update their PV agreements regarding data exchanges of ICSRs for case processing to target the duplicates being created.

A.O.B

- The regulators announced that the amendments to EC Implementing Regulation (IR) 520/2012 on the performance of pharmacovigilance activities are currently being finalised by the EC. The final amended IR will likely be published in the first half of 2025. As signal detection activities are concerned, the pilot of continuous monitoring in EudraVigilance by MAHs will be extended beyond the end of 2024 until the final IR comes into force. Thereafter the pilot will be closed. GVP IX will be amended to reflect this update.

- Finally, the regulators updated on the changes to PV fees following the European Parliament and Council revised EMA Fee Regulation in September 2023. Final adoption and formal publication on 7 February 2024 - Regulation (EU) 2024/568, implementation date foreseen for 1 January 2025. They presented high-level changes and benefits for marketing authorisation holders and have pointed out to a set of documents which are being updated and will be made available on EMA's fee website under the section 'New Fee Regulation' in November 2024.

  www.ema.europa.eu/en/documents/presentation/presentation-industry-platform-meeting-operation-eu-pharmacovigilance-m-rivera-vargas-p-lopez-fernandez_en.pdf

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.