Multi-stakeholder workshop on Pharmacogenomics

24 September 2024
Hybrid meeting / EMA, Amsterdam

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On 24 September 2024, the European Commission (EC), the Heads of Medicines Agencies (HMA), and the European Medicines Agency (EMA) organised a hybrid workshop to discuss how pharmacogenomics can help guide patients' treatment, contribute to the safety of medicines, and promote the implementation of pharmacogenomics in clinical practice.

This initiative is in line with the strategic goals set out in the EMA Regulatory Science to 2025, the European medicines agencies network strategy to 2025, and the current workplan of the joint HMA/EMA Big Data Steering group (BDSG).

The event was open to all stakeholders, either on-site or virtually, to facilitate active participation. It was broadcasted and recorded, and the speakers' slides and recordings are available on the EMA website.

This report captures the content of the presentations, discussions, and Question & Answer sessions, and includes recommendations on the next steps to promote a wider implementation of pharmacogenomics in the European Union (EU).

Introductions

The event was opened by Emer Cooke, Executive Director of the EMA, and by Irene Norstedt, Director responsible for the Directorate "People: Health & Society" within the DG for Research and Innovation at the European Commission.

Emer Cooke welcomed the audience and highlighted the progress that has been made in the field of pharmacogenomics. However, regulators, researchers, patients, and healthcare providers still face a range of challenges that need to be tackled. Irene Norstedt provided an overview of the European Commission's activities in support of the development of personalised medicine, by establishing policy and coordination initiatives at both the European and international levels. The European Commission has invested over two billion euros in collaborative research in personalised medicine over the last decade. As a major funder, the European Commission is looking for impact, such as improved patient experience and better treatment outcomes.

Emmanuel Cormier, head of the Regulatory Science and Innovation Task Force at EMA, provided an outline of the event and introduced the workshop objectives as follows:

- Identify priority areas for additional regulatory action to promote the clinical implementation of pharmacogenomics.
- Discuss how medicines regulators can facilitate the uptake of genomics by national healthcare systems.
- Discuss how to leverage genomic data linked to real-world data sources with examples of current studies using such data.
- Discuss how to increase the regulatory impact of EU-funded projects in personalised medicine.

Session 1: Pharmacogenomics – current regulatory state of play and areas that would benefit from additional action

Co-chairs: Niklas Blomberg (Innovative Health Initiative, Belgium) and Jessica Mwinyi (Medical Products Agency, Sweden)

Speakers: María J. Lamas (Agency for Medicines and Health Products, Spain), Marc Maliepaard (Medicines Evaluation Board, The Netherlands) and María Gordillo Marañon (Agency for Medicines and Health Products, Spain)

The first session highlighted the importance of pharmacogenomics for public health. Adverse drug reactions (ADRs) are an important cause of hospitalisations and deaths worldwide and contribute to higher healthcare costs. Furthermore, the risk of ADRs can increase with polypharmacy, which is associated with the aging global population. Pre-emptive pharmacogenomic testing (genotyping performed before medicine prescribing) can identify actionable genetic variants, prevent undesired ADRs, and have an impact on healthcare-associated costs. The EU-funded PREPARE study, an open-label trial, implemented a 12-gene panel that showed a ~30% reduction in risk of ADRs in both actionable and non-actionable genes.[1] Further data investigation that adjusted for an imbalance between study arms suggested that the risk reduction for actionable variants could be higher; this finding will need confirmation in an independent study. Future goals include generating real-world pharmacogenomic evidence, including variant information in regulation, and integrating omics data into electronic health records. This would allow the inclusion of pharmacogenomic biomarkers within the scope of pharmacovigilance. A revision of the standard ISO ICH E2B(R3) could enable the inclusion of omics data (e.g., genomics, proteomics, and metabolomics) from patients in ICSRs (Individual Case Safety Report).

The first EU pharmacogenomics guideline was published in 2012, and since then, pharmacogenomic information has been included in the Summary of Product Characteristics (SmPC) of an increasing

[1] A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study - ScienceDirect

number of centrally authorised medicinal products, including products that strictly require pre-treatment pharmacogenomic testing. The EMA is developing a repository of centrally authorised medicinal products with pharmacogenomic information in their SmPC. As of December 2023, approximately 24% of centrally authorised medicinal products contained pharmacogenomic information in their SmPC, with the majority being medicines indicated for oncology. Pharmacogenomic information can be found in different sections of the SmPC, depending on the impact and level of evidence of the association between pharmacogenomic determinants and drug response. It will be important to continuously update the SmPC with pharmacogenomic data obtained post-authorisation and to make such information more comprehensive for healthcare practitioners.

Session 2: Implementation of pharmacogenomics by healthcare systems

Co-chairs: Falk Ehmann (EMA) and Carmen Laplaza Santos (DG Research and Innovation, European Commission)

Speakers: Adrián Llerena Ruiz (Extremadura University, Spain), Munir Pirmohamed (University of Liverpool, United Kingdom), Jolyce Bourgeois (Belgian Health Care Knowledge Centre, Belgium), and Catharina Scholl (Federal Institute for Drugs and Medical Devices, Germany)

Session two provided examples of pharmacogenomic implementation activities in Spain, the United Kingdom (UK), Belgium and Germany. Spain has taken active steps towards implementing pharmacogenomics in its national healthcare system. Pharmacogenomic biomarkers have been included in the Spanish healthcare system's portfolio since 2023, and a pilot project in the Extremadura region (MedeA) will evaluate the clinical implementation of such biomarkers through the use of real-world data and electronic health records.

A successful example of implementation of pharmacogenomics in clinical practice in the UK is the reduction of abacavir-induced hypersensitivity reactions from 5% to 1% through pre-emptive HLA (Human Leukocyte Antigen) testing that should be preferred to reactive testing. A challenge highlighted by most speakers is the lack of pharmacogenomic information in clinical guidelines, with an example provided on the cytochrome *CYP2C19* polymorphism and clopidogrel response. The UK National Health Service (NHS) PROGRESS programme focuses on identifying individuals who would benefit from pharmacogenomic testing, the type of test that should be administered, and the support needed for doctors. The challenges that remain are the update of product information with pharmacogenomic information, the update of clinical practice guidelines, the embedding of pharmacogenomic information into electronic health records, creating an intelligent decision-support system to help physicians, the regulation of pharmacogenomic tests, and the demonstration of cost-effectiveness for the NHS.

An analysis of pharmacogenomic testing in Belgium by the Health Care Knowledge Centre (KCE) indicated that the Belgian healthcare system reimburses around twenty pharmacogenetic tests without restriction for the prescribing physician, though the test must be approved and performed by one of eight centres of human genetics. The analysis also highlighted that the recommendations produced by pharmacogenomic expert consortia (e.g., Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG)) are often not reflected in clinical practice guidelines. Moreover, the clinical benefit and cost-effectiveness of pre-emptive panel testing seems uncertain, including technical and practical barriers (e.g. with information sharing across institutions). In fact, pre-emptive panel testing is currently not reimbursed by the Belgian healthcare system.

Some challenges regarding the translation of pharmacogenomics into clinical practice in Germany were presented, such as the lack of clinical infrastructure with standardised workflows from prescribing to testing to the interpretation of results, the lack of knowledge and education on pharmacogenomics for healthcare providers, the presence of ethical and data protection concerns, and the need for a legal framework (e.g., pre-emptive testing). In general, no reimbursement is envisioned for pharmacogenomic testing due to a perceived lack of information in product information (i.e., whether the test is required, recommended, or informative only) as well as insufficient cost-effectiveness studies for testing in different indications. A new national initiative in Germany, GenomDE, aims to introduce genomic medicine into standard care to establish genetically confirmed diagnoses and to enable preventive measures and tailored therapies for rare and oncological diseases.

Session 3: How to leverage genomic data for evidence generation

Co-chairs: Patrice Verpillat (EMA) & Aimad Torqui (Medicines Evaluation Board (MEB), The Netherlands)

Speakers: Magnus Ingelman-Sundberg (Karolinska Institutet, Sweden), Sulev Reisberg (Tartu University, Estonia), Daniel Prieto-Alhambra (Oxford University, UK; Erasmus MC University, The Netherlands), Junqing Xie (Oxford University, UK), Stefania Simou (EMA)

Session three covered the complexities of clinical pharmacogenomic studies, considerations regarding genomic data sources and data types, pharmacogenomics studies using real-world data, and an overview of the HMA-EMA Catalogues on Real-World Data sources and studies.[2]

The need for generating more robust pharmacogenomic evidence to establish firm phenotype-genotype relationships was highlighted, bearing in mind the placebo effect in unblinded pharmacogenomic clinical studies. It was also mentioned that this is applicable to already authorised medicinal products where pharmacogenomic investigations are lacking. The lack of alignment in pharmacogenomic recommendations between regulators (FDA, EMA) and with consortia (CPIC, DPWG) was also raised; as well as the limited availability of actionable pharmacogenomic information in SmPCs. These issues contribute to the complexity of interpreting pharmacogenomic data and underline the importance of raising awareness and improving training for healthcare providers. A question on polygenic risk scores and their potential role in ADRs was posed, to which it was agreed that polygenic risk scores are still under investigation, and that it is more feasible to focus efforts on established gene-medicine pairs.

In addition to pharmacogenomic clinical studies, various genetic sequencing technologies and their potential limitations were discussed, with an emphasis put on the promising capabilities of long-read sequencing to detect structural variants which play an important role in pharmacogenomics. The cost of the infrastructure required to sequence, process and store genomic data was also mentioned.

Furthermore, real-world pharmacogenomics studies were presented as an important pilar in the triangulation of evidence to better inform clinical decision-making. The lack of standardised electronic health records and genomic information was brought forward. This limitation impedes the generation of real-world pharmacogenomic evidence at scale; however, existing biobanks (bearing in mind their intrinsic limitations such as phenotyping and the granularity of disease coding) can provide a way forward (e.g., UK Biobank, All of Us Research Programme). The Estonian Biobank was presented as an example where linkage can be used to study, identify, and report back pharmacogenomic findings to participants. It was also acknowledged that the rate of ADRs may be under-represented in clinical records. Finally, the opportunity arising from initiatives like the Yellow Card Biobank were briefly discussed, where a sample of patients with reported ADRs will be invited and genotyped.[3]

The HMA-EMA Catalogues on Real-World Data sources and studies were introduced as a tool to identify adequate data sources to perform studies where both individual genetic and phenotypic information are linkable for large population studies, such as the ongoing DARWIN EU® pharmacogenomic study investigating the association between certain genetic polymorphisms and the risk of myopathy among statin users.[4] Pharmacogenomic post-authorisation safety studies from industry are also recorded in the Catalogues. These study records often include a protocol and study results which are publicly available to view and download.

[2] Homepage | HMA-EMA Catalogues of real-world data sources and studies

[3] Yellow Card biobank | Making medicines and medical devices safer

[4] DARWIN EU® - Association between genetic polymorphisms of interest and risk of myopathy among statin users | HMA-EMA Catalogues of real-world data sources and studies

Session 4: The future of pharmacogenomics – next steps, challenges for implementation

Co-chairs: Peter Arlett (EMA) & Irene Norstedt (DG Research and Innovation, European Commission)

François Houÿez (Eurordis) shared a patient's perspective highlighting the challenges faced by families when genetic testing is not readily available. One case involved a woman with breast cancer whose surgeon opted for immediate tumour removal rather than waiting for genetic testing, which might have influenced treatment options. François Houÿez stressed the need for genetic testing to be accessible in all health centres to ensure timely care and emphasised the importance of genetic counselling. He suggested that regulators could play a greater role in regulating the time it takes for patients to receive their pharmacogenomic test results. Educating patients about their results is also essential so they can inform their families.

Vera Deneer (Utrecht University Medical Center, The Netherlands) shared a healthcare professional's perspective emphasising that pharmacogenomic testing should become a routine part of patient care, with a focus on large panel pre-emptive testing. She remarked that patients are increasingly aware of the role that genomics plays in ADRs, and many seek information on testing. She believes that healthcare professionals should be involved in all relevant activities, including guideline drafting. She also stressed the crucial need for harmonising pharmacogenomic guidelines (such as from the EMA, CPIC, DPWG), and aligning pharmacogenomic guidelines with product information. She highlighted that information sharing and education for healthcare professionals is essential; and that pharmacogenomic testing should be supported by all stakeholders, and local implementation at hospitals should be explored.

George P. Patrinos (University of Patras, Greece) provided a perspective from academia where he emphasised that pharmacogenomics should be standard practice but noted that academic research often fails to reach the clinic, necessitating better integration. He explained that economic evaluations, such as cost-effectiveness and cost-utility analyses, are crucial to support clinical research outcomes. He stated that the PREPARE study included such economic analyses, both at an individual country level as well as in an ongoing multinational analysis, which he believes demonstrates the importance of pharmacogenomics in terms of clinical safety and cost-effectiveness.[5] He believes that prospective clinical studies are needed and noted discrepancies in pharmacogenomic education across European universities. He also stressed that harmonising regulatory guidance is essential among regulatory agencies, like the FDA, the EMA, the PMDA, and others, as is raising public awareness, and ethical reimbursement practices.

Jesse Swen (Leiden University Medical Center, The Netherlands) provided an additional perspective from academia where he highlighted several challenges and opportunities. He noted the issue of missing heritability and the focus on pharmacokinetics over pharmacodynamics. He stressed that more research, such as cost-effectiveness studies, and funding are needed, especially for older medicines that lack comprehensive pharmacogenomic information compared to newer medicines. He highlighted the need for harmonising pharmacogenomic data in product information and testing; and developing infrastructure for result exchange within the healthcare chain. He also noted the importance of regulation with the example of *DPYD* testing that increased by 76% in Europe following EMA's recommendations.

Juan Riese Jorda (EP PerMed) summarised the objectives and activities of the European Partnership for Personalised Medicine towards the implementation of personalised medicine in public healthcare.[6] This involves mapping best practices in the development of personalised medicine, providing training, and creating awareness and engagement among healthcare professionals and policymakers. Its goal is to accelerate the integration of personalised medicine approaches into healthcare systems to improve patient outcomes and ensure sustainable healthcare practices. He highlighted the need for regulators and health policymakers to be informed and involved in these efforts.

[5] A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study - ScienceDirect

[6] Home - European Partnership for Personalised Medicine - EP PerMed

Marius Garmhausen (EFPIA) provided an industry perspective where he highlighted the difficulty of getting access to high-quality real-world data. He noted that initiatives exist to improve this, but that incentives should be created for pharmaceutical companies to generate real-world evidence during medicine development rather than post-approval. He highlighted that simplifying processes is crucial and proposed that regulators provide guidance on the filing process, clarify evidence expectations, and establish a clear transparency framework.

Jessica Mwinyi (Medical Products Agency (MPA), Sweden) provided a regulatory perspective where she highlighted the fragmentation of pharmacogenomics across the EU, with varying degrees of implementation in member states. She noted pharmacogenomic guideline differences between countries and consortia and discussed harmonising regulation through unified guidelines and standardised protocols for pharmacogenomic testing to ensure consistent implementation across countries. She highlighted the need for clearer pharmacogenomic labelling of medication and promoted cross-border data sharing to support personalised medicine initiatives.

The panellists agreed on the need for systematic data collection and testing across diseases to gain broader insights into pharmacogenomic evidence generation, which are relevant actions enabling the implementation of pharmacogenomics.

Furthermore, the inclusion of pharmacogenomic information in product labels, along with timely updates to the authorised medicinal products' SmPC based on emerging data from literature and trials, are considered important enabling factors. Equally critical is the availability of harmonised and clear guidance on where specific information should be included in the label and its associated actions, recommendations, or consequences. The SmPC currently focuses on the effects of the medicine at a population level, but for the clinician, individual level pharmacogenomic data is more relevant. The European Public Assessment Reports (EPARs) could serve as a potential source for this information. This led to the proposed action of enhancing transparency regarding the evidence required to include actionable pharmacogenomic information in the SmPC.

Improving training and education to healthcare professionals and other relevant parties was also discussed. This session reiterated the need for better data collection, regulatory transparency, and timely updated product information to integrate pharmacogenomics into clinical practice effectively.

Recommendations on pharmacogenomics in medicines regulation and on implementation into clinical practice

Priority areas for additional regulatory action:

1. Optimise the availability of pharmacogenomic information for approved medicines, informing pharmacogenomic-guided treatments.

2. Make clear recommendations on how and where actionable pharmacogenomic information should be included in the product information and other relevant regulatory documents.

3. Foster alignment in pharmacogenomic regulatory recommendations between international regulators in collaboration with learned societies.

4. Further include pharmacogenomics in the scope of pharmacovigilance by updating the guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products and through exploring changes to the standard of electronic transmission of Individual Case Safety Reports (ICSRs).

Facilitating the uptake of genomics by national healthcare systems:

1. Implement comprehensive education and training programmes for healthcare professionals, people working in industry, and regulators to maximise the successful integration of pharmacogenomic information into clinical practice.

2. Encourage pre-emptive genetic testing (genotyping performed before medicine prescribing), enabling better patient management and integration of pharmacogenomic individual data into electronic health records.

3. Gather evidence and share cost-effectiveness data of pharmacogenomic-based treatment options and consider recommendations for the implementation of identified cost-effective pharmacogenomic-guided treatments.

Leverage genomic data linked to real-world data sources:

1. Enable insights and actionable knowledge by linking pharmacogenomic data to other real-world data during medicines development as well as in the post-authorisation phase.

2. Promote the sharing of cross-border data by leveraging the European Health Data Space (EHDS) to harness the increasing amount of pharmacogenomic information and integrate it with other sources of data, such as electronic health records.

Increase the impact of EU-funded projects:

1. Foster the inclusion of findings of publicly funded research into pharmacogenomic-guided treatment.

2. Launch funding calls for evidence generation on pharmacogenomic-guided treatment including cost-effectiveness assessments. This should include consultation with regulators and downstream decision-makers on the methodology and actionable outcomes before engaging in studies. Examples of such studies include outcome-focused studies aimed at establishing robust phenotype-genotype relationships.