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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the guideline revision on good pharmacogenomic practice

Agreed by Methodology Working Party (MWP)	August 2025
Adopted by CHMP for release for consultation	01 December 2025
Start of public consultation	09 December 2025
End of consultation (deadline for comments)	31 March 2026

The proposed revised guideline will replace the 'Guideline on good pharmacogenomic practice' (EMA/CHMP/718998/2016).

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support .

Keywords	Pharmacogenomics, good practices, pharmacogenomic analyses, biomarkers, study design, pharmacokinetics, DNA sequencing

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Introduction

Since its initial publication in 2018, the guideline on good pharmacogenomic practice has played a crucial role in shaping best practices, ensuring consistency, and providing a clear framework for regulators and stakeholders. As anticipated at the time of its implementation, the field of genomics has continued to evolve, driven by scientific advancements, technological innovations, and emerging regulatory considerations.

To reflect these developments, it is essential to revise the guideline on good pharmacogenomic practice, incorporating new evidence, methodologies, and best practices. By doing so, this guideline revision seeks to provide regulators and stakeholders with an improved framework that supports the highest standards of practice while fostering innovation and progress.

This guideline revision will take into account feedback from experts, recent scientific discoveries, and lessons learnt from the application of the initial guideline. The revised document will aim to maintain its core objectives while integrating improvements that align with the latest advancements in the field.

1. Problem statement

Scientific advancements in the field of pharmacogenomics necessitate a revision of the existing guideline to ensure its continued relevance and applicability. In addition to incorporating new scientific knowledge, this revision aims to provide greater clarity on topics already covered, facilitating more precise and actionable guidance for regulators and stakeholders.

The issues requiring major revisions or inclusion of new guidance are:

1. Pharmacogenomic methodology
    a. Sequencing technologies
    b. Specific analytical issues
        i. Polymorphic genes & substrate specificity
        ii. Deoxyribonucleic acid (DNA) variants in subpopulations
        iii. Proficiency testing
2. Interpretations and recommendations
    a. Phenotype and genotype correlations
    b. General versus specific medicinal product use recommendations
3. Reporting and nomenclature
4. Pharmacogenomic study design
    a. Interventional studies
    b. Non-interventional studies

2. Discussion (on the problem statement)

By integrating the following critical revisions, the revised guideline aims to provide a more comprehensive and scientifically rigorous framework for pharmacogenomic applications in medicines development, regulatory decision-making, and clinical practice:

1. Pharmacogenomic methodology

a. Sequencing technologies

Improvements in sequencing technologies, particularly the ability to generate longer reads, now allow for a more accurate distinction between complex gene structures, such as hybrid genes or genes with high sequence homology. These advancements have significant implications for the identification and interpretation of pharmacogenetic variants. The revised guideline will therefore include aspects on the usage of third generation long read sequencing and will include aspects on quality control measures that were not elaborated on previously. Direct ribonucleic acid (RNA) sequencing and epigenetic sequencing are not within the scope of the guideline.

b. Specific analytical considerations

i. Polymorphic genes & substrate specificity

Cytochrome P450 (CYP) enzymes, such as the enzyme CYP2D6, are highly polymorphic and play a crucial role in metabolising a wide range of xenobiotics, including medicinal products, environmental chemicals, and dietary compounds. With over 170 haplotypes identified, *CYP2D6* polymorphisms pose significant analytical challenges, necessitating specialised approaches which will be addressed in the revised guideline.

Metabolising enzymes of active substances can exhibit specificity, which describes an enzyme's affinity to bind to different substrates (i.e., medicines). Substrate specificity is crucial when a DNA variant leads to reduced enzymatic function, as e.g. seen in intermediate metabolisers (IMs). In these cases, the degree of functional impairment relative to the wild-type enzyme can vary depending on the specific medicinal product being metabolised. In this guideline revision, special attention will be paid to the CYP3A4/CYP3A5 interplay. Given that both enzymes share a substantial number of substrates and that a notable proportion of people of European ancestry carry a non-functional *CYP3A5* allele[1], this should be carefully considered both during medicines development and regulatory assessments (pre- and post-marketing).

ii. DNA variants in subpopulations

In recent years, increasing awareness of the differences in DNA variants across ancestries has necessitated a re-evaluation of how such data is interpreted and applied in pharmacogenomics. Genetic ancestry plays a crucial role in influencing interindividual variations in medicinal product exposure and response, as different genetic variants associated with ancestry can impact benefit-risk profiles. This variability challenges the conventional approach of testing for only the most common variants within broadly defined populations and calls for a more refined, population-specific strategy for variant selection. To ensure both safe medicines development and appropriate post-market pharmacovigilance strategies, it is essential to incorporate relevant pharmacogenomic data and genetic characteristics of different populations into the product information, thereby enabling optimal treatment regardless of genetic background. The revised guideline will address these complexities and provide recommendations on integrating pharmacogenomic differences across populations into medicines development practices.

iii. Proficiency testing

The guideline revision will include information on appropriate allelic testing, including quality requirements.

2. Interpretations and recommendations

a. Phenotype and genotype correlations

The revised guideline will expand on phenotype and genotype correlations and how they translate to clinical recommendations.

b. General versus specific medicinal product use recommendations

Greater clarity is needed regarding general versus specific medicinal product use recommendations before and after market authorisation. When a medicinal product is predominantly metabolised by a single pharmacogene product, it is essential to ensure that all non-functional variants of that gene are incorporated into safety protocols. If specific dosing recommendations are based on specific DNA variants or haplotypes, this must be explicitly stated. In such cases, a precise understanding of the *1 (wild type) designation in pharmacogenes is paramount to avoid misinterpretation and ensure accurate clinical guidance.

3. Reporting and nomenclature

Unambiguous allele and genotype nomenclature is essential for regulatory assessments (pre- and post-marketing), as its absence significantly impairs the interpretation of pharmacogenomic results and hampers the determination of appropriate dose adjustments.

The revised guideline will:
1) Provide guidance on the proper use of internationally accepted allele and genotype nomenclature for pharmacogenes and their haplotypes.
2) Recommend internationally recognised sources for identifying and defining pharmacogenetically relevant genotypes and associated phenotypes.

The nomenclature used in the guideline must be corrected and refined, and above all used consistently. Overall, it should reflect an awareness that a large proportion of genetic variation remains unsampled and not all functionally relevant variants are known.

Definitions will be provided for terms such as "variant," "mutation," "polymorphism," and "single nucleotide polymorphism." And while this is reflected in the current version of the guideline, the wording around "common" and "rare" variants should be more carefully chosen to reflect our increasing understanding that variant frequencies differ across populations, and that the interpretation of frequency thresholds must therefore be applied cautiously and in relation to diverse populations.

4. Pharmacogenomic study design

a. Interventional studies

The revised guideline will provide recommendations on when and how to best utilise pharmacogenomics in clinical development from Phase 0 to Phase IV. It will be a comprehensive reference for designing interventional studies that takes the connections between genetic variability and medicines safety and efficacy into account. Special emphasis will be placed on referring to existing guidelines, such as the 'ICH M12 Guideline on the investigation of drug interactions', the 'EMA/CHMP/37646/2009 Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products', and the 'EMA/446337/2011 Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection' in relevant sections and providing an overarching context for when they are applicable. Topics covered in detail will include:

- Utilising pharmacokinetic/pharmacodynamic data to support genotype-guided dosing (including discussions on sparse sampling, modelling approaches, and selection of relevant clinical endpoints)
- Specifics of randomised controlled trials (RCTs) in establishing genotype-medicinal product response relationships (e.g., sample size planning, power for rare variant analysis, multiple testing correction)
- Complex trial designs such as enrichment designs, adaptive designs, and master protocols
- genome-wide association studies in an RCT setting
- Incorporating pharmacogenomic findings into the product information

b. Non-interventional studies

The revised guideline will include a section on how real-world data (RWD) related to pharmacogenomics can be generated and utilised, an addition to the current version of the guideline.

Non-interventional studies using RWD can provide insights on populations for whom information from interventional studies is limited or missing, including but not limited to different ethnic groups, age, patients with comorbidities such as renal or hepatic impairment, patients taking co-medication (long-term), and patients at risk for rare adverse drug reactions (EMA/99865/2025 Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence for regulatory purposes). RWD may also be used to expand knowledge on RW/clinical outcomes of trial populations, or support identification of suitable trial populations for pharmacogenomic studies.

3. Recommendation

Considering the points identified above, the Methodology Working Party (MWP) recommends revising the guideline on good pharmacogenomic practice.

4. Proposed timetable

Release of draft concept paper for public consultation in Q4 2025, with a deadline for comments in Q1 2026. Finalisation of concept paper in Q2 2026, and adoption of concept paper expected in Q3 2026 by the Committee for Medicinal Products for Human Use (CHMP).

Release of draft guideline for public consultation in 2027, and a workshop with external participants. Finalisation of guideline in 2028.

5. Resource requirements for preparation

A temporary Drafting Group for the guideline revision will be established and will be composed of both MWP members and Methodology European Specialised Expert Community (ESEC) members. Regular monthly meetings will be scheduled to advance the drafting of the guideline and monitor progress. Input from MWP, scientific Committees (CHMP, Pharmacovigilance Risk Assessment Committee (PRAC), Committee for Advanced Therapies (CAT)) and Working Parties (Scientific Advice Working Party (SAWP) and Oncology Working Party (ONCWP)) will be requested throughout when needed. The need for a workshop is anticipated for 2027.

6. Impact assessment (anticipated)

The guideline will enhance the understanding of methodological concepts and challenges in the field of pharmacogenomics. It will outline best practices for pharmacogenomics, ensuring consistency, and providing a clear framework for regulators and stakeholders, which is anticipated to benefit public health.

7. Interested parties

Guidance on this topic is expected to be important to the following Committees and Working Parties who will be consulted prior to the release of the draft guideline: CHMP, PRAC, CAT, SAWP and ONCWP. Input from industry, academia, and healthcare professionals will be gathered through public consultation and further facilitated via a dedicated workshop with external stakeholders in 2027.

8. References to literature, guidelines, etc.

References to literature:

[1] CYP3A4 and CYP3A5 Genotyping Recommendations: A Joint Consensus Recommendation of the Association for Molecular Pathology, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, and Pharmacogenomics Knowledgebase; Victoria M. Pratt, Larisa H. Cavallari, Makenzie L. Fulmer, Andrea Gaedigk, Houda Hachad, Yuan Ji, Lisa V. Kalman, Reynold C. Ly, Ann M. Moyer, Stuart A. Scott, Ron H.N. van Schaik, Michelle Whirl-Carrillo, Karen E. Weck; The Journal of Molecular Diagnostics, 2023.

References to guidelines and other documents:

See Guideline on good pharmacogenomic practice for the current version of the guideline on good pharmacogenomic practice.

See ICH M12 Guideline on drug interaction studies_Step 5 for the ICH M12 Guideline on the investigation of drug interactions.

See Guideline on key aspects for the use of pharmacogenomics in the pharmacovigilance of medicinal products.

See Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection.

See Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence for regulatory purposes