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Committee for Human Medicine Products / Methodology Working Party
Human Medicines Division

Draft consolidated 3-year rolling work plan for the Methodology Working Party

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Work plan period: January 2026 – December 2028 (reviewed on a yearly basis)

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1. Strategic goals

1.1. Short-term strategic goal

Ensure that Methodology Working Party (MWP) supports the work of all Committees and provides methodological guidance across the medicine's development lifecycle.

1.2. Long-term strategic goals

In alignment with the European medicines agencies network strategy to 2028, MWP aims to leverage the cross-disciplinary expertise to support methodological innovation in global drug development and support advice and interpretation of complex methodology across drug development.

The following are the main strategic goals:

1. Provide the required and state-of-the-art methodological support to the operational work of the European Medicines Regulatory Network (EMRN) now and in the future with an emphasis on product related support upon request from Committees, the Scientific Advice Working Party (SAWP) and the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD(h)).
2. Deliver appropriate guidance documents to support and improve the development and authorisation of medicines, based on experience gained assessing products and providing scientific advice as well as based on the most recent scientific and methodological insights.
3. Raise the understanding of all aspects of methodology for non-specialist assessors and ensure appropriate development of all assessors across the EU Network through knowledge transfer of experience gained from key assessments, as well as developing appropriate training.
4. Develop and leverage a strong expertise network including academic and learned society collaborations to increase competence across the EU network of methodological assessors.
5. Strive for methodological excellence across the EU Network to ensure best methodological practice in assessment and advice procedures, and to produce credible model-based evidence that supports medicine development and regulatory decisions.
6. Develop an appropriate quantitative evidence assessment framework to assess uncertainty when multiple sources of data are integrated, including the use of modelling and artificial intelligence for such integration.
7. Ensure the EU is recognised globally as a region of excellence in all aspects of methodology as applied to the regulation of medicines and to provide a leading voice in international collaboration efforts.

2. Tactical goals

2.1. Guidance activities

In general, the guideline activities, including implementation, support strategic objectives 2, 3 and 5. MWP primarily orders its guideline activities according to the leading methodological discipline; all these disciplines have demonstrated to be relevant across the full medicinal product lifecycle – even if some disciplines are currently more prominent for pre-clinical or early clinical development evidence, and others more for late-stage clinical and life cycle management. In the past years of MWP operation it has become clear that an increasing number of guidance developments benefit from a designated

multi-disciplinary focus. For new guidance activities (starting in 2026 or later) this is clearly indicated. The methodological areas are presented in alphabetical order below.

Biomarkers and diagnostic medicinal products

Biomarkers are instrumental for the quantitative and qualitative understanding of cellular physiological and pathophysiological processes and mechanisms of drug efficacy as well as toxicity, the latter related to projected risks of an adverse drug reaction (ADR). Biomarker research and development is currently a key component in the development of personalised medicines in a global setting, especially, but not only, for oncological treatments. As a result, the number of biomarker-guided oncological medicinal products is rapidly increasing. Therefore, more regulatory focus has been placed on pivotal clinical trials on the analytical methods used for predictive biomarker measurement (candidate companion diagnostics) as well as on methodological approaches used to demonstrate an improved benefit-risk relationship for such biomarker-guided therapeutics.

Nowadays, diagnostic medicinal products and in particular diagnostic imaging represents a broad and complex field of medicine. Medicinal products developed for diagnostic imaging (especially radiopharmaceuticals) are being increasingly tested not only to support the initial diagnosis of a disease, but also for patient selection for targeted treatment (theranostics), to monitor treatment outcomes, as a predictive and prognostic markers, for image-guided therapies (e.g., image-guided radionuclide therapy), in pre- and intra-operative situations to localise a pathology, etc.

Overall, the research field concerning biomarkers and diagnostic medicinal products is highly dynamic and therefore poses particular challenges for EMA and the national competent authorities. In particular, the need for new guidance, revision of existing guidance, cross-Domain collaboration, bilateral exchanges with other international regulatory agencies, dialogue with stakeholders and finally support of assessors, e.g., via trainings, will be key focus areas.

Biostatistics

The implementation of the estimand framework outlined in ICH E9 (R1) will result in updating language and concepts in many EU guidelines. The objective of these updates is to ensure clarity on the scientific questions addressed by clinical trials and ensure that these trials, along with the associated statistical inference, are adequately poised to support corresponding conclusions, in order to improve the robustness and clarity of regulatory decision making.

Across the clinical research landscape, how trials are designed and conducted is changing with an increasing number of proposals utilising tools such as master protocols, adaptive components and Bayesian methods. Especially in rare diseases the use of control data external to the clinical trial is considered. There is a need for new guidance in these areas to ensure these novel approaches are used in appropriate settings, can be evaluated and meet the required evidentiary standards as well as improve quality and efficiency of drug development. This will aid their integration into our established system for benefit-risk assessment, balancing innovation with stringent safety and efficacy criteria. These innovations are related to and need to be supported by the planned updates of existing guidelines, which leads to the prioritised work over the next 3 years.

Clinical Pharmacology

Bridging with pharmacokinetic data is a focus area for MWP, and the Clinical Pharmacology Operational Expert Group (OEG) continues to develop guidelines to clarify EMA requirements for generics of more recent innovator products. Increasing complexity is encountered when abridged applications are made to increasingly complicated formulations, e. g., long acting injectables, locally acting agents, biologicals (biosimilars), possibility of making synthetic copies of biological drugs, etc. To address issues arising in this area, multidisciplinary work is needed, not only with the quality domain, but also with clinical

working parties, the non-clinical working party as well as other regulatory expertise. It is also essential that EU guidance is consistent with globally adopted positions at ICH.

Data management and analytical capability

Excellent data quality, data interoperability and highly-structured data are crucial for all data sources that inform regulatory assessment. Foundational activities related to ensuring this are for example the development of a European Technical Implementation Guide complying with ICH M11, and drafting estimand and analysis data concepts to be integrated in a unified logical model for clinical trial data.

Unlocking the potential of data for regulatory decision-making and doing so consistently throughout the EMRN will require a high level of appropriate (data) standardisation, interoperability and analytical capability. MWP will contribute to building a strong foundation for clinical study data standardisation and analytics by ensuring regulatory relevance of planned pilots on interactive tabulation and visualisation of clinical study data, contributing to guidance related to clinical study data submissions, e.g. clinical trial data standards, and fostering capacity building through knowledge sharing activities within the Methodology European Specialised Expert Community (ESEC).

Data Science & Artificial Intelligence (AI)

Given the rapid development in the field of AI/machine learning (ML) applied to the medicinal product lifecycle, there is an urgent need for regulatory support and engagement, preferably based on guidance. The work will be building on the finalised EMA reflection paper on the use of AI in this domain. Further guidance will be needed to support assessment as well as to support leveraging the innovative potential whilst assuring the required evidentiary standard for regulatory decision making.

The focus is on guidance areas that are most urgent and provide opportunity to have impact. Standardisation of terminology and principles is essential and instrumental to all future guidance. Collaboration on this with other regulatory jurisdictions (esp. FDA and PMDA) is foreseen to ensure progress and immediate relevance to industry. Furthermore, initial focus is on the use of AI in clinical development. Secondly, guidance on the use of AI in pharmacovigilance may be developed in conjunction with the Pharmacovigilance Risk Assessment Committee (PRAC). As this is a fast-moving field, further guidance may be added when there will be sufficient regulatory experience on relevant related topics.

Modelling & Simulation (M&S)

The implementation of model-informed drug development is a key area of work for MWP. This includes expanding beyond the description of drug exposure, towards the dynamic description of complex drug effects and disease subtypes and progressions. Additional regulatory experience on Physiologically Based Pharmacokinetic Modelling (PBPK) has been gained since the publication of the PBPK guideline. There is need for up-to-date guidance on mechanistic modelling, and to reflect on the experience since introduction of the PBPK guideline. The integrated nature of modelling necessitates multi-disciplinary collaboration across expert areas, working parties (i.e. quality, non-clinical & 3Rs), and committees (such as the Paediatric Committee (PDCO)).

Real-World Evidence

Following finalisation of the reflection paper on the use of Real-World Data (RWD) in non-interventional studies to generate Real-World Evidence (RWE), a roadmap was developed with the aim to identify and prioritise further guidance development for the use of RWD in areas other than non-interventional studies. It also includes a summary of existing guidance on RWD/RWE across regulatory jurisdictions as well as areas for potential future guidance. Based on gaps identified, several of these topics will be

developed, most probably in a multi-disciplinary setting as they, e.g., may relate to clinical trials, modelling, biomarker development or safety monitoring.

(A) Activities ongoing

Multidisciplinary

- Concept paper on the development of a reflection paper on the use of external controls for evidence generation in regulatory decision-making (i.e. Biostatistics and RWE)

Biomarkers and diagnostic medicinal products

- Guideline on predictive biomarker assay development in the context of medicinal product lifecycle
- Concept Paper on the revision of the guideline on good pharmacogenomic practice
- Concept paper on the revision of the guideline on clinical evaluation of diagnostic agents and the Appendix 1 on diagnostic imaging

Biostatistics

- Reflection Paper on the use of Bayesian methods in clinical development
- Reflection Paper on platform trials
- Revision of the guideline on multiplicity issues in clinical trials
- Guideline on non-inferiority and equivalence comparisons in clinical trials
- Q&A on small populations, including Q&A on indirect comparisons

Clinical Pharmacology

- Q&A and new guideline on food effect assessment and drug interactions in the gastrointestinal tract (topics not included in the ICH M12 guideline on drug interaction studies)
- PSBGLs as and when requested by CMD(h)

Data Science & AI

- AI terminology and principles (in collaboration with FDA)

Modelling and Simulation

- Concept paper on assessment and reporting of mechanistic models used in the context of model informed drug development

RWE

- Q&A on the use of real-world data including patient registries for regulatory purposes

(B) Activities to be started in 2026

Multidisciplinary

- Guidance on assessment and reporting of mechanistic models used in the context of model-informed drug development (i.e. Biostatistics, Clinical Pharmacology and M&S)

- Reflection paper on the use of external controls for evidence generation in regulatory decision-making (i.e. Biostatistics and RWE)
- Q&A to be read in conjunction with the baseline covariates guideline to take into account the use of synthetic covariates (i.e. Biostatistics and RWE)
- Guidance on physiologically-based pharmacokinetic (PBPK) modelling (i.e. Clinical Pharmacology and M&S)

Biomarkers and diagnostic medicinal products

- Revision of the guideline on good pharmacogenomic practice
- Review of the D80 clinical assessment report template to better incorporate pharmacogenomics in assessments
- Revision of the guideline on clinical evaluation of diagnostic agents and the Appendix 1 on diagnostic imaging

Biostatistics

- Revision of the guideline on missing data in confirmatory trials to implement ICH E9 (R1)

Clinical Pharmacology

- Reflection paper on the clinical pharmacology package for oligonucleotides
- Review and revision of guidelines impacted by ICH M13A (final) and M13B/C when finalised
- PSBGLs: new guidelines proposed by CMD(h), SAWP, assessors, or external stakeholders

Data Science & AI

- Guidance on AI in clinical development
- Guidance on AI in pharmacovigilance (in conjunction with PRAC)

Modelling & Simulation

- Q&A on study design for pivotal PK(/PD) trials in paediatric patients

RWE

- Review and revision of the guideline on registry-based studies

(C) Activities to be started later

Multidisciplinary

- Concept paper on the use of the evidence assessment framework for decision making (i.e. Biostatistics, Data Science & AI, M&S, RWE)
- Q&A on model-informed dose finding/selection (i.e. Biostatistics and M&S)
- Q&A on the use of synthetic data in regulatory submissions (i.e. Biostatistics, M&S, and RWE)
- Concept paper on the use of pragmatic trials in regulatory decision making (i.e. Biostatistics and RWE)
- Guidance on missing data in non-interventional studies (i.e. Biostatistics & RWE)

- Guidance on use of modelling & simulation in bioequivalence (i.e. Clinical Pharmacology and M&S)
- Guidance on the clinical pharmacology of peptides (i.e. Clinical Pharmacology and M&S)
- Guidance on renal impairment, e.g. on estimation of eGFR and handling of renal function in models and SmPC recommendations (i.e. Clinical Pharmacology and clinical expertise from the Immunology and Rheumatology WP)

Biomarkers and diagnostic medicinal products

- Revision of guidelines identified in 2026 that are in need of revision

Biostatistics

- Revision of adaptive designs guidance to take into account ICH E20
- Guidance on how to align estimand attributes across different trials in the context of a meta-analysis

Clinical Pharmacology

- Guidance on the clinical pharmacology information in the SmPC, with a particular focus on drug-drug interactions (Sections 4.4, 4.5, 5.2) (i.e. in collaboration with the Working Group on Quality Review of Documents)

Modelling & Simulation

- Q&A on methodological aspects of model-informed cardiac risk assessment

Ongoing MWP support to ICH guidelines

MWP typically assesses the impact of newly or soon to be adopted methodological ICH guidelines on existing EMA guidance documents. If action is needed for any guidance, this is included above in the (A), (B) or (C) lists. In addition, MWP members are usually involved in implementation planning and activities.

Implementation

- ICH E9 (R1) – Estimands & sensitivity analysis
- ICH E11A – Paediatric extrapolation
- ICH M12 – Drug-drug interactions
- ICH M13A - Bioequivalence

Development and Implementation

- ICH E20 – Adaptive designs
- ICH E21 – Pregnant and breast feeding individuals
- ICH E22 – Patient preference studies
- ICH M11 - Clinical electronic structured harmonised protocol
- ICH M13B/C - Bioequivalence
- ICH M15 – Model-informed drug development

- ICH E23 – Considerations for the Use of Real-World Evidence (RWE) to Inform Regulatory Decision Making with a focus on Effectiveness of Medicines
- ICH M18 - Framework for Determining Utility of Comparative Efficacy Studies in Biosimilar Development Programs
- Natural History Studies and Registry Data to Advance Rare Disease Drug Development
- Annex to ICH Q5E - Comparability of Advanced Therapy Medicinal Products (ATMPs) Subject to Changes in Their Manufacturing Process
- ICH Q1/Q5 on stability studies

2.2. Training and workshop activities

- Training on ICH M13A – Assessment of bioequivalence studies
- Training on ICH E11A - Extrapolation for paediatrics (2026)
- Training on ICH M15 – General principles for model-informed drug development (2026)
- AI Masterclass (2026)
- Training on statistical methodology applied at quality level
- Training on the updated guideline on requirements for demonstration therapeutic equivalence between OIPs for asthma and COPD
- Training on well-established use
- Workshop on multiplicity (2026)
- Workshop on predictive biomarker assay development (2026)
- Workshop on good pharmacogenomic practice (2027)
- Workshop on clinical evaluation of diagnostic agents/diagnostic imaging (2026)
- Workshop on model informed bioequivalence and model-informed approaches for bridging across formulations (2027)

2.3. Communication and Stakeholder activities

2.3.1. European level

- Annual interested parties' meeting (virtual)
- Involved in planning and participation in ACT EU and NDSG workshops, when topics align with the MWP workplan
- Interaction with EU-funded research projects, including More-EUROPA, INVENTS, ERAMET and RealiseD
- Continue to engage in discussions regarding the use of open-source software
- Engage in change management related to the revised pharmaceutical legislation

2.3.2. International level

- Continue to engage in Cluster meetings with international Regulatory Agencies as appropriate

- Work with international regulators as appropriate to provide guidance on AI terminology and high-level key principles
- Foster opportunities to engage and exchange with international regulatory colleagues

2.4. Multidisciplinary collaboration

- Support development of clinical guidelines
- Support Biologics Working Party (BWP) guideline development
- Support Biosimilar Medicines Working Party (BMWP) ongoing guidance updates
- Foster collaboration and support Non-clinical and 3Rs Working Parties (NCWP & 3RsWP) in the area of AI, (predictive) biomarkers, and modelling and simulation approaches in the context of New Approach Methodologies (NAMs)
- Actively engage with GCP Inspectors Working Group, especially in the area of AI
- Support SAWP with updates to Questions and Answers: Qualification of digital technology-based methodologies to support approval of medicinal products
- Foster closer link with Quality Innovation Group, especially in the area of AI and M&S
- Foster collaboration with the Pharmacovigilance Risk Assessment Committee (PRAC), especially in the areas of AI and patient registries
- Support the implementation of key projects of the EMRN, including the outputs of the pilot on clinical study data analysis
- Determine the target operating model, the capacity and capability requirements of the EMRN, and the technical requirements to receive, validate, store, manage and analyse raw data
- Move towards a risk-based approach for assessment of methodology based on the MIDD evidence assessment framework
- Collaboration with QWP in the development of product-specific bioequivalence guidance and the use of Physiologically Based Biopharmaceutical Modelling (PBBM) in setting clinically relevant specifications, and in the area of comparing quality attributes

3. Operational goals

3.1. Pre-submission activities

3.2. Evaluation and supervision activities

Methodology Working Party will continue to provide product related support upon request from Committees and SAWP. The scope will cover all areas of expertise and will ensure collaborative support that moves beyond the narrower boundaries of established disciplines. Additionally, there will be dedicated and systematic support to:

SAWP in the area of Biostatistics and RWE;

SAWP and PDCO in Modelling & Simulation;

CMD(h) for the development of product specific bioequivalence guidelines.

4. List of Abbreviations

ACT EU: Accelerating Clinical Trials in the European Union

ADR: Adverse Drug Reaction

AI/ML: Artificial Intelligence/Machine Learning

BMWP: Biosimilar Medicines Working Party

CMD(h): Coordination Group for Mutual Recognition and Decentralised Procedures – Human

EMA: European Medicines Agency

EMRN: European Medicines Regulatory Network

GCP: Good Clinical Practice

GL: Guideline

ICH: International Council for Harmonisation

M&S: Modelling & Simulation

MIDD: Model-Informed Drug Development

MWP: Methodology Working Party

NDSG: Network Data Steering Group

PBPK: Physiologically Based Pharmacokinetic Modelling

PBBM: Physiologically Based Biopharmaceutical Modelling

PDCO: Paediatric Committee

PRAC: Pharmacovigilance Risk Assessment Committee

PSBGL: Product-Specific Bioequivalence Guidelines

Q&A: Questions and Answers

QWP: Quality Working Party

RWD: Real-World Data

RWE: Real-World Evidence

SAWP: Scientific Advice Working Party

SmPC: Summary of Product Characteristics