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4 Draft revised consolidated 3-year work plan for the 5 Methodology Working Party (MWP)

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9 Work plan period: May 2022 – December 2024

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1. Strategic goals

The Methodology Working Party aims to leverage the cross-disciplinary expertise to support methodological innovation in global drug development and support advice and interpretation of complex methodology across (clinical) drug development. The following are the main strategic goals.

- Provide the required and state-of-the-art methodological support to the operational work of the European Medicines Regulatory Network (hereafter, the 'EU Network') now and in the future with an emphasis on product related support upon request from Committees, SAWP and CMD(h).
- 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.
- Raise the understanding of all aspects of methodology for non-specialist assessors and ensure appropriate development of junior assessors across the EU Network through knowledge transfer of experience gained from key assessments, as well as developing appropriate training.
- Develop and leverage a strong expertise network including academic and learned society collaborations to increase competence across the EU network of methodological assessors.
- Strive for methodological excellence across the EU Network to ensure best methodological practice in assessment and advice procedures.
- Ensure the EU is recognised globally as a region of operational 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: activities/projects to deliver the strategic goals

2.1. Guideline activities

2.1.1. Clinical Pharmacology

Pharmacokinetics

Bridging with pharmacokinetic data is a focus area for MWP, and a product specific bioequivalence guidance drafting group has been formed to continue developing product-specific bioequivalence guidelines to clarify EMA requirement for generics of more recent innovator products and controversial ones. 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.

MWP will support questions around the need for pharmacokinetic data for all kinds of applications. Clinical pharmacology expectations for many of the newer treatment modalities are not covered by current EMA guidelines, and there is a need to clarify the European expectations. A reflection paper on the clinical pharmacology package for oligonucleotides is a prioritised activity in the MWP work plan, and it is envisaged that something similar may be needed for other emerging treatment modalities (e.g., peptides).

MWP is also an important group to support the European position in the development of new ICH guidelines, for example in the clinical pharmacology area. In addition, MWP will oversee training activities and best practices in clinical pharmacology assessment.

High priority/short-term

- Reflection Paper on clinical pharmacology package for oligonucleotides.
- Q&A on implications of different salts in generic products (e.g., for sunitinib, dasatinib).
- Product Specific Bioequivalence Guidelines (PSBGLs) (multiple) in liaison with CMD(h): for 2024, azacitidine, budesonide (LALA GIT), trametinib, dabrafenib, paliperidone palmitate (3M depot) and melatonin have been prioritised as the next in series for drafting. In addition, PSBGLs will also be developed for albumin-bound paclitaxel, digoxin, methylphenidate and betahistine.

Long-term

- Harmonisation of the information on clinical pharmacology topics of the SmPC (e.g., DDI potential).
- Guidance on bridging requirements for well-established use applications.
- Q&A on food effect assessment and drug interactions in the gastrointestinal tract (topic not included in ICH M12 drug interaction guideline).
- Investigation of other methods for abridged applications of complicated formulations (multidisciplinary).

Guideline work led by other working parties

- Revision of the guideline on the requirements for clinical documentation for orally inhaled products (OIP).
- Guideline on the development and manufacturing of oligonucleotides.

Modelling and Simulation

Modelling and simulation is a rapidly evolving area in terms of both technologies and applications in drug development. The latter are expanding beyond the description of drug exposure, towards the dynamic description of complex drug effects and disease subtypes and progressions. Mechanistic models are also increasingly used in the context of drug development. Additional regulatory experience on Physiologically Based Pharmacokinetic Modelling (PBPK) has been gained since the publication of the PBPK GL. There is need for up-to-date guidance on Quantitative Systems Pharmacology (QSP) and to reflect on the experience since introduction of the PBPK GL. The integrated nature of complex modelling necessitates multi-disciplinary collaboration across expert areas, working parties, and committees (such as PDCO).

The planned concept papers will formulate problem statements for planned workshops and subsequent guidance documents will be informed and enriched by the outcome of discussions of workshops to be held in 2024.

The following activities, guidelines/papers and workshops are currently planned in order of time and priority.

High priority/short-term

- Concept Paper and/or Q&A on design, conduct, qualification and reporting and use of exposure response models (including QSP) in regulatory submissions.

- Q&A on reporting and qualification of Physiologically Based Pharmacokinetic Modelling (PBPK) models.

Long-term

- Q&A on model-informed dose finding/selection.
- Q&A on methodological aspects of model informed cardiac risk assessment.
- Concept Paper on Model informed bioequivalence (and biosimilarity).

Guideline work led by other working parties and committees

- Revision of Guidance on the investigation of medicinal products in the term and preterm neonate (EMEA/536810/2008)

2.1.2. Real World Evidence

MWP considered that guidance on the use of Real-World Data (RWD) to generate Real-World Evidence (RWE) in non-interventional studies is most urgent given the increasing use of this type of RWE in Marketing Authorisation Applications and consequent accrued experience on the topic.

Furthermore, a roadmap shall be developed with the aim to identify and prioritise further guidance development for the use of RWD in areas other than non-interventional studies. It will also include a summary of existing guidance on RWE across regulatory jurisdictions as well as areas for potential future guidance development in collaboration with the Methodology ESEC. Examples of future topics being considered include the use of RWD in the context of clinical trials, e.g., considerations of trial designs that prospectively include external control data. MWP will consider the best way to address such issues in a multi-disciplinary setting.

This results in the following priorities:

- Reflection Paper on the use of Real-World Data to generate Real-World Evidence in non-interventional studies.
- Roadmap for the development of RWE guidance.

2.1.3. Clinical Trial Modernisation

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 streamline the relevance of 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.

The landscape of trials being conducted is also changing with an increasing number of proposals utilising tools such as master protocols and Bayesian methods. There is a need for new guidance in these areas to ensure these novel approaches meet the required evidentiary standards and facilitate their evaluation. 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 following priorities.

High priority/short-term

- Revision of guideline on multiplicity issues in clinical trials.

- Reflection Paper on the use of single arm trials.
- Revision of guideline on the non-inferiority margin and the guideline on switching between superiority and non-inferiority into one guidance document.
- Reflection Paper on platform trials.
- Reflection Paper on Bayesian methods in clinical development.

Long-term

- Revision of guideline on missing data.
- Revision of small population guideline.

2.1.4. Pharmacogenomics for precision medicine

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). Predictive biomarker research and development is currently a key component in the development of personalized medicines in a global setting, in particular for oncological treatments. As a result, the number of predictive biomarker-guided oncological medicinal products is rapidly increasing. Therefore, more regulatory importance 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.

Overall, the research field concerning biomarkers is highly dynamic and therefore poses particular challenges for EMA and the respective national competent authorities. In particular, the need for new guidance, revision of existing guidance, bilateral exchanges with other international regulatory agencies, dialogue with stakeholders and finally support of assessors, e.g., by trainings.

The following priority guideline activities are currently planned and related stakeholder meetings and trainings may be part of the guideline drafting/revision processes:

- Guideline on predictive biomarker-based assay development in the context of drug development and lifecycle (EMA/CHMP/800914/2016).
- Revision of Good Pharmacogenomic Practice (EMA/CHMP/718998/2016).

2.1.5. Data Science and AI

Given the rapid development in the field of AI/ML applied to the medicinal product lifecycle, there is an urgent need for regulatory guidance. The work will be building on the finalised EMA reflection paper on the use of artificial intelligence in this domain.

Further specific guidance is required, and it is proposed to focus on two main guidance areas:

- Guideline on the use of AI in clinical development. Topics being considered include the use of AI/ML-applications for selecting study sites and study participants, machine-learning derived endpoints and covariates, and digital twin technology (intersecting with guidance on the use of real-world data).
- Guideline on the use of AI in pharmacovigilance.

2.1.6. Support to ICH activities

Many ICH activities are in areas where the EU expertise is anchored in MWP and the ESEC. MWP will continue to support development of ICH guidelines by providing expert input and support where necessary, including in E6(r3), E11A, E20, M12, M13, M14, M15 and others as required.

2.1.7. Non-guideline activities

The following activities will be actively supported by MWP:

- Develop a strong expertise network including academic collaborations to increase competence across the EU network of methodological assessors.
- Partner in the implementation of the priority recommendations of the HMA-EMA joint Big Data Steering Group, EMRN Network Strategy to 2025, EMA Regulatory Science to 2025 Strategy and ACT EU in the area of methodology, especially within the area of big data and Real-World evidence (RWE).
- Implement in the EU network ICH and EMA guidelines where MWP expertise is needed, e.g., ICH E9(R1) on estimands and sensitivity analysis in therapeutic area guidelines.
- Identify applications where M&S is/should be proposed as key aspect of the regulatory submissions, develop, or adapt the standards and implement a framework for optimal and highest quality regulatory input
- Engage with consortia developing mechanistic models (including quantitative systems pharmacology (QSP) and quantitative systems toxicology (QST) models) and consider their regulatory applications. Mechanistic QSP/QST models serve for gaining quantitative understanding of cellular physiological processes, mechanisms of toxicity, toxicodynamic biomarkers, or projected risk of an adverse drug reaction (ADR).
- Provide appropriate support to the EU network for generic/hybrid medicines including product-specific requirements.
- Develop the EU Network competence and collaborations to engage on model-based BE, by actively participating in an ongoing collaborative review of relevant cases, cooperating in global cluster meetings, and attracting and developing Subject Matter Expertise on this topic.
- Provide continued input to EC for revision of general pharmaceutical legislation.
- Support activity to improve/harmonize labelling in general.
- Support work on digitalized SmPC
- Review of EMA data quality framework (DQF) and follow-up chapter on implementation of DQF to RWD and other chapters as appropriate.
- Participation of Methodology ESEC members in the organisation of the workshop on RWE methodology (Q1 2024).

2.2. Training activities

2.2.1. Training

The Methodology domain will work closely with the European Network Training Centre (EU NTC) to deliver core grounding in methodology, advances and state of the art methodology, reflection of hot topics, and support of new regulatory developments.

Training will be provided on all new or revised guidance documents after they are developed. Its format will depend on the complexity and novelty of the document.

A revision of the topics for training will be made on a yearly basis to ensure that emergent training activities are provided.

Specific focus will be on the development and maintenance of curricula in data science, biostatistics, modelling and simulation and epidemiology, with close liaison with the Big Data Steering Group and EMA.

2.2.2. Workshops

Workshops identified to be initiated in 2024 and 2025

- EMA workshop on RWE methodology (Q1 2024)
- EMA workshop on mechanistic (Quantitative systems pharmacology/toxicology) exposure-response models in drug development. (Q2 2024)
- EMA workshop on Concept Paper on Bayesian statistics (Q3 2024)
- EMA workshop on PBPK (Q4 2024)
- EMA workshop in relation to the guideline on predictive biomarker-based assay development in the context of drug development and lifecycle (2024)
- EMA workshop on Model-based Bioequivalence and Model informed approaches for bridging across formulations (Q2 2025)
- EMA workshop on dose optimization (Q4 2025)

Workshops to be supported by MWP

MWP will support workshops being organised by other stakeholders, including Big Data Steering Group, ACT-EU, as well as events organised by other Interested Parties such as the EFSPI Regulatory Workshop and regulators from other jurisdictions.

2.3. Communication and stakeholder activities

- Maintain European Specialised Expert Communities (ESEC) activities in biostatistics, M&S, PK, and genomics, RWE, and AI
- Through the ESECs and Operational Expert Groups, ensure a bilateral flow of information regarding methodological issues identified in regulatory submissions, the content of guidelines, and proposals for new guidelines.
- Continue to have cluster meetings in the areas of biostatistics, pharmacometrics, genomics, generics, and RWE. These may also be with Health Canada, Japanese and Australian regulators and others depending on the area and interest.

- Annual meetings with relevant interested parties
- All relevant guidelines developed or revised will need to be supported by a workshop including industry, as appropriate.
- For the longer term it will be explored if interactions can be expanded to academic organisations with key roles in the drug development life cycle, professional organisations as well as patient representative organisations.
- Across the Methodology domain, members will be actively present in the scientific exchange and discussions on methodology in drug development and regulatory science, through publishing papers, presenting in conferences, and participating as discussants in workshops.
- To share international harmonised views, joint publications with regulatory opinion leaders from different jurisdictions are foreseen.
- Together with the Big Data Steering Group, create an EU Big Data 'stakeholder implementation forum.' Dialogue actively with key EU stakeholders, including patients, healthcare professionals, industry, HTA bodies, payers, device regulators and technology companies.
- Be mindful of the impact of forthcoming device legislation to ensure appropriate communication and stakeholder activities are initiated with Notified Bodies in particular setting the frame for AI software as a medical device and how that will affect borderline cases and medicines development.
- Establish key communication points in national competent authorities and build a resource of key messages and communication materials on regulation and methodology.

2.4. Multi-disciplinary collaboration

- A large number of therapeutic area-specific guidance documents are proposed that will be delivered by other working parties in other domains. Area specific knowledge will be required to specifically address methodological appropriateness. Broad representation across and exchange within the Methodology domain will be required to ensure sufficient coverage for the range of therapeutic areas.
- Cross-disciplinary work on the interplay between operations and methodology, especially for guidance developed by Good Clinical Practice Inspectors.
- Cross disciplinary work with Quality Working Party and other stakeholders on PBBM model assessment.
- In order to support adequate evaluation of model-based analyses MWP will aim to facilitate an increase in presence and visibility in relevant committees of methodological expertise from across the EU network such as CHMP, PRAC, PDCO, CMD(h) and CAT.
- In the area of modelling and simulation, knowledge transfer between MWP and the Big Data Steering Group and RWE initiatives.
- Methodology domain experts will be involved in relevant innovation meetings such as EMA's Innovation Task Force meetings with applicants.
- With respect to modelling and simulation, there is a need to contribute to Replacement, Reduction and Refinement (3Rs) of animal experiments work in the non-clinical domain. Statistical input may additionally be required.

- To deliver an improved access to raw data (e.g., clinical or pharmacometrics), it is proposed to actively engage with the Network Advisory Group on Raw Data with members across committees and working parties to examine the practical aspects of patient level data visualisation and analysis, with an initial focus on clinical trial data. Training will be required in processes and relevant software to facilitate this.
- Contribute to guidance being developed or to be developed for the implementation of the new medical devices legislation and establish criteria to determine the accuracy, precision, reliability and comparability of device-based diagnostic tests and other in vitro diagnostics.
- Contribute to guidance being developed or to be developed on device and internet-based solutions for outcome assessment as part of decentralised trials.
- Strengthen EU Network processes for big data submissions. Launch a 'Big Data learnings initiative' where submissions that include big data are tracked and outcomes reviewed, with learnings fed into reflection papers and guidelines. Enhance the existing EU PAS register to increase transparency on study methods.
- Establish the EU Network ability to assess applications supported by data science including AI models created through machine-learning algorithms.
- Propose regulatory research priorities for funders in across the activities of Methodology Working Party, including in the big data area. Maintain a list of research questions and propose a research agenda that is a living document.

3. Operational goals: medicinal product-specific activities

Methodology Working Party will provide product related support upon request from Committees and SAWP. The scope will cover the areas of expertise of previous WPs but also extend to additional areas as RWE and AI. This will ensure collaborative support that moves beyond the narrower boundaries of currently defined disciplines.

4. Tactical goals: activities/projects to deliver the strategic goals - Priorities for 2024

4.1. Guideline activities

4.1.1. Clinical Pharmacology

Pharmacokinetics

- RP on clinical pharmacology package for oligonucleotides.
- Q&A on implications of different salts in generic products (e.g., for sunitinib, dasatinib).
- Product Specific Bioequivalence Guidelines (PSBGLs) (multiple) in liaison with CMD(h): for 2024, azacitidine, budesonide (LALA GIT), trametinib, dabrafenib, paliperidone palmitate (3M depot) and melatonin have been prioritised as the next in series for drafting. In addition, PSBGLs will also be developed for albumin-bound paclitaxel, digoxin, methylphenidate and betahistine.

Modelling and Simulation

- CP and/or Q&A on design, conduct, qualification and reporting and use of exposure response models (including QSP) in regulatory submissions.

- Q&A on reporting and qualification of Physiologically Based Pharmacokinetic Modelling (PBPK) models.

4.1.2. Real World Evidence

- RP on the use of Real-World Data to generate Real-World Evidence in non-interventional studies.
- Roadmap for the development of RWE guidance.

4.1.3. Clinical Trial Modernisation

- Revision of guideline on multiplicity issues in clinical trials.
- RP on the use of single arm trials.
- Revision of guideline on the non-inferiority margin and the guideline on switching between superiority and non-inferiority into one guidance document.
- RP on platform trials.
- RP on Bayesian methods in clinical development.

4.1.4. Pharmacogenomics for precision medicine

- Guideline on predictive biomarker-based assay development in the context of drug development and lifecycle (EMA/CHMP/800914/2016).
- Revision of Good Pharmacogenomic Practice (EMA/CHMP/718998/2016).

4.1.5. Data Science and AI

- Guideline on the use of AI in clinical development.
- Guideline on the use of AI in pharmacovigilance.

4.1.6. Support to ICH activities

MWP will continue to support development of ICH guidelines by providing expert input and support where necessary, including in E6(r3), E11A, E20, M12, M13, M14, M15 and others as required.

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- EMA workshop in relation to the guideline on predictive biomarker-based assay development in the context of drug development and lifecycle (2024)

4.3. Communication and Stakeholder activities

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- A large number of therapeutic area-specific guidance documents are proposed that will be delivered by other working parties in other domains. Area specific knowledge will be required to specifically address methodological appropriateness. Broad representation across and exchange within the Methodology domain will be required to ensure sufficient coverage for the range of therapeutic areas.
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- In the area of modelling and simulation, knowledge transfer between MWP and the Big Data Steering Group and real-world data initiatives.
- Methodology domain experts will be involved in relevant meetings such as EMA's Innovation Taskforce meetings with companies.
- With respect to modelling and simulation, there is a need to contribute to Replacement, Reduction and Refinement (3Rs) of animal experiments work in the non-clinical domain. Statistical input may additionally be required.
- To deliver an improved access to raw data (e.g., clinical or pharmacometrics), it is proposed to actively engage with the Network Advisory Group on Raw Data with members across committees and working parties to examine the practical aspects of patient level data visualisation and analysis, with an initial focus on clinical trial data. Training will be required in processes and relevant software to facilitate this.
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learnings fed into reflection papers and guidelines. Enhance the existing EU PAS register to increase transparency on study methods.

- Establish the EU Network ability to assess applications supported by data science including AI models created through machine-learning algorithms.
- Propose regulatory research priorities for funders in across the activities of Methodology Working Party, including in the big data area. Maintain a list of research questions and propose a research agenda that is a living document.

4.3.2. European level

- Maintain European Specialised Expert Communities (ESEC) activities in biostatistics, M&S, PK, and genomics, RWE, and AI.
- Through the ESECs and Operational Expert Groups, ensure a bilateral flow of information regarding methodological issues identified in regulatory submissions, the content of guidelines, and proposals for new guidelines.
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- Be mindful of the impact of forthcoming device legislation to ensure appropriate communication and stakeholder activities are initiated with Notified Bodies in particular setting the frame for AI software as a medical device and how that will affect borderline cases and medicines development.
- Establish key communication points in national competent authorities and build a resource of key messages and communication materials on regulation and methodology.

4.3.3. International level

- Continue to have cluster meetings in the areas of biostatistics, pharmacometrics, genomics, generics, and RWE. These may also be with Health Canada, Japanese and Australian regulators and others depending on the area and interest.

4.3.4. Industry level

- Annual meetings with relevant interested parties.
- All relevant guidelines developed or revised will need to be supported by a workshop including industry, as appropriate.
- For the longer term it will be explored if interactions can be expanded to academic organisations with key roles in the drug development life cycle, professional organisations as well as patient representative organisations.
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