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Human Medicines Division

Consolidated 3-year work plan for the Methodology Working Party (MWP)

Chairperson:	Kit Roes
Vice chair:	Kristin Karlsson

Work plan period: May 2022 – December 2024 (with a first review point after one year)

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Strategic goals

The new 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 (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

- Revision of Guidance on the role of pharmacokinetics in the development of medicinal products in the paediatric population, EMEA/CHMP/EWP/147013/2004.
- Question and Answer (Q&A) on model informed posology recommendations for PD1-PDL1 inhibitors.
- Q&A on methodological aspects of model informed cardiac risk assessment.
- Q&A on reporting and qualification of Physiologically Based Pharmacokinetic Modelling (PBPK) models.
- 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 2022, bosutinib, 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 fampridine, metformin, lurasonide, azacitidine, pirfenidone and betahistine.

- Q&A on Replacement of rifampicin in drug-drug interaction studies.
- Finalisation of Reflection Paper (RP) on investigation of pharmacokinetics and pharmacodynamics in the obese population (EMA/CHMP/535116/2016) following public consultation in 2018.
- RP on clinical pharmacology package for oligonucleotides.
- CP on Model informed bioequivalence.
- Finalisation of revision of the guideline on the requirements for clinical documentation for orally inhaled products (OIP).
- Guidance on immunogenicity testing for generic/hybrid peptides.
- CP and/or Q&A on reporting and qualification of QSP models.
- Q&A on model-informed dose finding/selection.
- CP on the use of modelling and simulation (M&S) to support Summary of product characteristics (SmPC) claims in the absence of dedicated clinical studies.
- CP on design, conduct, reporting and use of exposure response analyses in regulatory submissions.
- Q&A on M&S in support of drug development in neonates.
- Q&A on food effect assessment and drug interactions in the gastrointestinal tract.

2.1.2. Real World Evidence

- CP on the use of Real World Evidence for regulatory decision making.
- Roadmap for the development of RWE guidance.

2.1.3. Clinical Trial Modernisation (including ICH E9 implementation)

- 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 possibly the guideline on switching between superiority and non-inferiority.
- Revision of guideline on missing data.
- RP on bayesian methods in clinical development.
- Revision of small population guideline.
- RP on platform trials.

2.1.4. Pharmacogenomics for precision medicine

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

2.1.5. Other

- Reflection paper on the use of Artificial Intelligence (AI) in medicines development.

2.1.6. Non-guidelines 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.
- Help implement the priority recommendations of the HMA-EMA joint Big Data Task Force, EMRN Network Strategy to 2025, EMA Regulatory Science to 2025 Strategy and ACT EU in the area of analytics, especially within the area of big data and real world evidence (RWE).
- Develop EU Network competence and specialist collaborations to engage with big data.
- Implemente in the EU network of ICH and EMA guidelines where MWP expertise is needed, e.g. ICH E9(R1) on estimands and sensitivity analysis in therapeutic area guidelines.
- Collaborate to establish a dedicated framework for the development of relevant documentation for AI.
- 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.
- Improve the labelling (precision medicine) and lifecycle management of medicinal products especially by the use of M&S tools and other methods/technologies.
- Engage with consortia developing quantitative systems pharmacology (QSP) and quantitative systems toxicology (QST) models and consider their regulatory applications. QST models contain the characterization of pharmacokinetics and toxicokinetics (PBPK/PBTK modelling), a quantitative understanding of cellular physiological processes, mechanisms of toxicity, toxicodynamic biomarkers, and 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.

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 guidelines after they are developed. Its format will depend on the complexity and novelty of the guideline.

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 2022-23:

- Patient registries that fulfil regulatory needs.
- Real World Evidence international symposium.
- Guidelines being developed or revised may require a workshop depending on the complexity and novelty of the guideline.
- Workshop joint with clinical domain but anchored in methodology on Single Arm Trials.
- ACT EU Workshop on methodological challenges.
- Physiologically based biopharmaceutical modelling (PBBM) with industry and international regulators.

Workshops to be initiated in 2023 if capacity allows:

- Quantitative systems pharmacology/toxicology.

2.3. Communication and stakeholder activities

- Establish and maintain European Specialised Expert Communities (ESEC) activities in biostatistics, M&S, PK, and genomics building on the communities of the previous working parties. Launch activities in RWE, AI and others as necessary.
- 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 industry organisations are required across all relevant disciplines. Five (one per discipline) envisaged per year.
- 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 guidances 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 more narrow boundaries of currently defined disciplines.

Priorities for 2022 – 2023

4. Tactical goals: activities/projects to deliver the strategic goals

4.1. Guideline activities

4.1.1. Clinical Pharmacology

- Revision of Guidance on the role of pharmacokinetics in the development of medicinal products in the paediatric population, EMEA/CHMP/EWP/147013/2004.
- Q&A on model informed posology recommendations for PD1-PDL1 inhibitors.
- Q&A on implications of different salts in generic products (e.g. for sunitinib, dasatinib).
- Q&A Replacement of rifampicin in drug-drug interaction studies.
- Finalisation of Reflection paper on investigation of pharmacokinetics and pharmacodynamics in the obese population (EMA/CHMP/535116/2016) following public consultation in 2018.
- Q&A on M&S in support of drug development in neonates.
- CP on Model informed bioequivalence.

4.1.2. Real World Evidence

- CP on the use of RWE for regulatory decision making.

- Roadmap for development or RWE guidance.

4.1.3. Clinical Trial Modernisation (inc ICH E9 implementation)

- 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,
- RP on bayesian methods in clinical development.
- RP on platform trials.

4.1.4. PGx for precision medicine

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

4.1.5. Other

- Reflection paper on the use of AI in medicines development.

4.2. Training activities

The Methodology domain will work closely with the 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 guidelines after they are developed. The format of these trainings will depend on the complexity and novelty of the guideline.

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.

Workshops identified to be initiated in 2022-23

- Workshop on patient registries that fulfil regulatory needs.
- Real World Evidence international symposium.
- Guidelines being developed or revised may require a workshop depending on the complexity and novelty of the guideline.
- Workshop joint with clinical domain but anchored in methodology on Single Arm Trials.
- ACT-EU Workshop on methodological challenges.
- Workshop on Physiologically based biopharmaceutical modelling (PBBM) with industry and international regulators.

Workshops to be initiated in 2023 if capacity allows

- Quantitative systems pharmacology/toxicology.

4.3. Communication and Stakeholder activities

4.3.1. Multi-disciplinary collaboration.

- A large number of therapeutic area-specific guidance documents are likely to be proposed that will be delivered by other domains. Area specific knowledge will be required to specifically address methodological appropriateness. Broad representation across and exchange within the 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 guidances developed by Good Clinical Practice Inspectors.
- Cross disciplinary work with Quality Working Party and other stakeholders on PBBM model assessment.
- 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 pharmacometric) , it is proposed to instigate an 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 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.
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- 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 MWP, 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

- Establish and maintain ESEC activities in biostatistics, modelling & simulation, pharmacokinetics, genomics building on the communities of the previous working parties. Launch activities in Real World Evidence, Artificial Intelligence and others as necessary.
- 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.
- 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.

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. These will be held quarterly.
- To share international harmonised views, joint publications with regulatory opinion leaders from different jurisdictions are foreseen.

4.3.4. Industry level

- Annual meetings with relevant industry organisations are required across all relevant disciplines. Five (one per discipline) envisaged per year.
- 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.