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MWP Stakeholder Interaction Meeting Report

7 December 2023

Role	Name
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1. Summary

Following the opening of the public consultation on the draft Methodology Working Party (MWP) workplan for 2024, a virtual MWP stakeholder interaction meeting took place on 7 December 2023.

The main objectives of this meeting were:

- to consolidate the comments received during the public consultation (from 1 until 30 November 2023) on the draft version of the MWP workplan 2024 which constitutes the roadmap of MWP activities on the basis of the priorities that have been identified.
- to shape the final updated MWP workplan for endorsement by the Committee for Human Medicinal Products (CHMP). The adoption of the workplan by CHMP will set the roadmap of the MWP activities for 2024.

2. Introduction to the Methodology Working Party and its 3-year workplan

The MWP Chairs introduced the structure and organization of the Methodology Domain, highlighting the role and interplay of the MWP, the various (temporary) Operational Expert Groups (OEG) and Drafting Groups (DG) as well as the European Specialised Expert Community (ESEC) for Methodology.

The current scientific interest areas of the Methodology ESEC were outlined and comprise of biostatistics, modelling and simulation, clinical pharmacology, pharmacogenomics, artificial intelligence and data science, and real-world evidence.

The important role of the ESEC to act as a platform for capacity building and knowledge sharing across the European Medicines Regulatory network (EMRN) was emphasized.

The 3-year workplan of MWP (2022-2024) aimed to implement the following 5 strategic goals of MWP for each of the identified scientific areas of interest:

- Operational support to Committees and working parties
- Development of guidance documents
- Increase the knowledge sharing capacity within the Methodology ESEC
- Strengthen the network of expertise across the National Competent Authorities and with academia
- Remain a leading voice in global collaborations with International regulatory partners

To ensure high quality decision making in a rapidly developing environment, the following key areas for guidance were identified by MWP:

- Clinical Pharmacology
- Real World Evidence (RWE)
- Clinical Trial Modernisation
- Pharmacogenomics
- Data Science & Artificial Intelligence (AI)

2.1. Conclusion

The importance of creating and maintaining a multilayer network to support assessors within the EMRN and to advance on methodological topics was emphasized and current ways of working were outlined. Priorities for guidance development were shared and stakeholder feedback was sought on these through a public consultation.

3. Discussion on activities for clinical pharmacology

It was clarified that elements in the guideline on the investigation of Bioequivalence (BE) will be iteratively revised to specifically address aspects not covered by the different parts of the ICH M13 guideline series (M13A, M13B and M13C). The revision taking into account M13A will begin shortly. Similarly, the relevantly impacted product specific bioequivalence guidelines (PSBGLs) will be updated when the ICH M13 guidelines come into effect.

The need for implementation of the estimand framework was discussed. MWP will reflect on which other guidelines beyond therapeutic area specific ones will need to be revised in order to implement the estimand framework.

MWP will aim at producing more technical reflections in form of e.g., Q&As to accompany high-level ICH documents.

The importance of enabling paediatric development by the various MWP activities was emphasized and acknowledged. MWP will continue to collaborate with other EMA working parties and committees (e.g. also PDCO) in producing helpful guidance to applicants which is often motivated by commonly seen questions and comments to applicants.

Although training development is not outlined in detail in the workplan, it is of high importance to MWP and modules with regulatory focus will be developed and delivered.

4. Discussion on activities for real world evidence

The planned roadmap for the development of RWE guidance will take into consideration other RWE-related guidance documents (e.g. on registry studies, the data quality framework and meta-data catalogues) or planned activities (e.g. related ICH documents) while further interaction and alignment across related initiatives and communities will be ensured (i.e. with DARWIN EU and the Methodology ESEC).

Future guidance documents shall also cover aspects related to the estimand framework and target trial emulation and further reflections on RWE application in case of small populations could be addressed at related future workshops with a focus on RWE methods. It was noted that the use of external controls is out of scope of the single arm reflection paper but is very much an area that MWP recognises as suitable for guidance development and will be considered for inclusion in the in the new 3-year work plan for 2025-2027.

5. Discussion on activities for clinical trial modernisation

Given the multiple methodological areas in need of guidance, either revised or newly drafted, MWP outlined its immediate priorities.

Emphasis was put on the need to implement the estimand framework in various EU guidelines and to provide guidance on emerging concepts and technologies such as AI, platform trials, Bayesian methods, use of external controls or single arm trials.

Long-term plans, including revising guidelines on adaptive designs, covariate adjustment, meta-analysis, missing data and small populations as well as new guidance on validation of novel digital endpoints and trials with pragmatic elements, will be outlined in more details in the work plan for 2025-2027.

Feedback on specific topics for existing/future drafting groups will be taken into account and future stakeholder interactions will foresee the possibility of content-related dialogue in dedicated workshops as well as public consultations on draft guidance documents.

It was brought to the attention of MWP that computational costs might be high for the use of Bayesian methods (which could also be applicable to areas like artificial intelligence and data science). It was worth

mentioning that at this stage in time, the choice of statistical method lies with the sponsor and is not imposed by EMA.

A roadmap for clinical trial modernization, the need to highlight the interplay between different activities and to further improve the collaboration across Domains were deemed important and MWP confirmed that EU positions are regularly shared and discussed with international regulators (i.e. US FDA, PMDA & HC) during cluster meetings.

6. Discussion on activities for pharmacogenomics

The need for more guidance, dialogue, and training in the field of predictive biomarker-based assay development was emphasised.

MWP clarified that the scope of the guideline on predictive biomarker-based assay development in the context of drug development and lifecycle will cover all kind of predictive biomarkers (i.e. genomic, genetic, proteomic) and corresponding biomarker assay formats.

While patient reported outcomes, surrogate endpoint validation and paediatric population aspects are generally applicable to all kind of biomarkers and the scope of the revision of the guideline on good pharmacogenomic practice will focus on PGx aspects only, attention will be paid to cover related aspects in the guideline as needed.

7. Discussion on activities for data science and AI

MWP will focus on the finalization of the reflection paper on AI and aims to provide guidance in an appropriate format for the use of AI in clinical development and pharmacovigilance.

MWP will aim to harmonise the use of technical terms with EU and international regulators.

8. General comments

The importance of supporting drug development in paediatric populations and for rare diseases as well as of aligning guidelines as much as possible were emphasised and MWP reiterated its plans to collaborate with Health Technology Assessments, Clinical Trials Coordination Group, Accelerating Clinical Trials in the EU (ACT EU) and research initiatives (e.g. Innovative Medicines Initiative (IMI) projects) as much as possible.

9. Next steps

Accounting for the comments received during the public consultation of the revised 2024 workplan, MWP will finalise the document and will start drafting the 3-year workplan for 2025-2027.