December 2015
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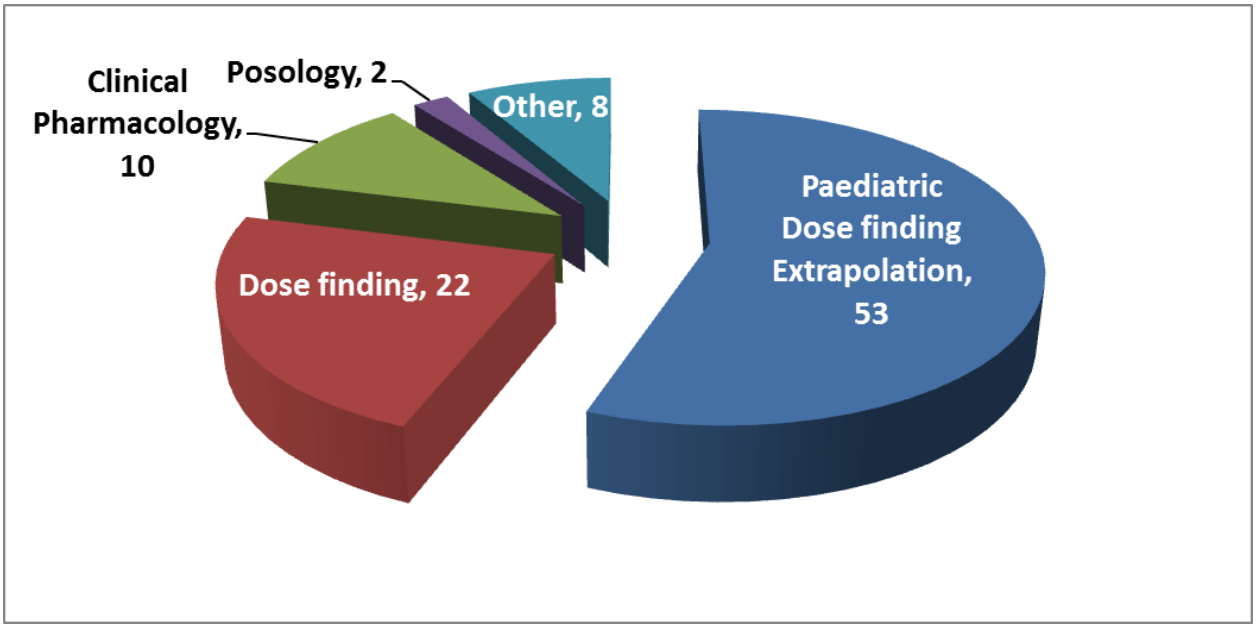
2015 Activity report of the Modelling and simulation working group (MSWG)

Background

The Modelling and Simulation Working Group (MSWG) was established in January 2013 to provide specialist scientific support to the SAWP, PDCO and CHMP in the form of feedback on technical issues around how companies propose to use modelling and simulation in support of registration dossiers. The drivers for establishing such a group came from both internal and external sources.

From January 2015 to December 2015, 90 procedures were referred to the MSWG with 47 from PDCO, 37 from SAWP, 2 from CHMP, 1 from CMDh and 3 Guidelines. A breakdown of the scope of questions addressed by M&S is shown in the pie chart below:

Scope of M&S in regulatory submissions as experienced by MSWG.



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Paediatric Dose Finding/Extrapolation

Models with the inclusion of covariates to account for growth and maturation or any other characteristics are used to extend and characterise the PK/PD relationship from adults to other groups or between different paediatric age groups. Based on the projected PK (/PD) in children and the clinical context, decisions are made on the paediatric doses, uncertainties regarding benefit risk in paediatric age groups, and the need for further investigations i.e. further PK/PD studies, and or need to generate clinical efficacy/safety data.

Dose finding strategy

The convening of the MSWG has facilitated technical evaluation of the M&S approaches proposed by companies at a stage in drug development when CHMP can influence company decisions (i.e, too late at the time of MAA). Because dose finding is traditionally considered of low/medium regulatory impact as it is superseded by pivotal efficacy and safety data (although high risk for the company), these reviews could be considered as "enabling innovation". This is only partly true, however, as it also has important impact on the benefit/risk decision since inadequate understanding of the dose-exposure-response relationship is often a concern during the assessment of new medicines, and could result in poor posology recommendations in SmPC, and post approval commitments. As modelling approaches are more efficient, they are also more likely to result in optimal dose selection with increased chances of success at phase III and enable of a more thorough characterisation of dose exposure response relationships at the time of MAA.

The value of M&S in dose-exposure-response characterisation and dose selection was discussed in the EMA-EFPIA workshop on dose finding. (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2014/06/event_detail_000993.jsp&mid=WC0b01ac058004d5c3)

Clinical Pharmacology

The role of population pharmacokinetics and PBPK in clinical pharmacology evaluations is acknowledged in several regulatory guidelines. It is envisaged that growing experience and qualification of models will enable in the future wider regulatory acceptance of M&S in clinical pharmacology.

Posology

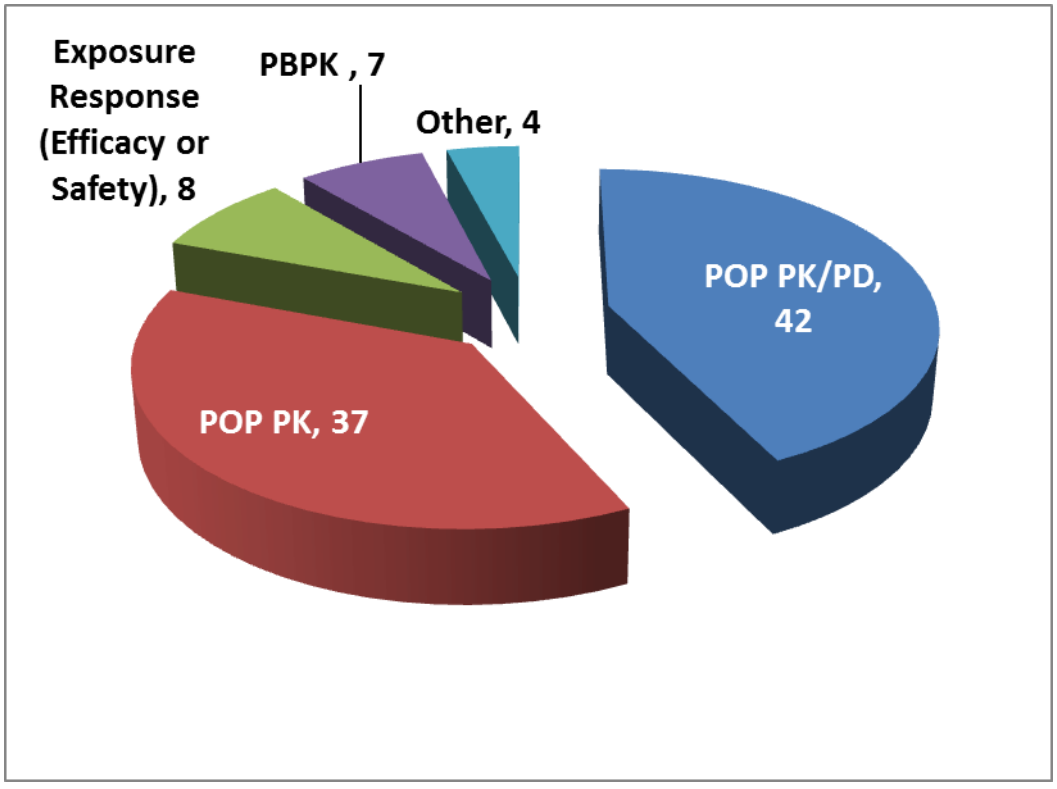
This refers to the use of dose exposure response analyses and/or PK/PD modelling to support different doses or/and regimens to the ones tested in pivotal trials.

Other

Other uses of M&S as experienced by MSWG in 2015 include simulation of concentrations in target compartment, first in man dose selection, use of PK/PD modelling in support of bio-similarity, use of PBPK to justify a bio waiver for an additional strength and use of POP PK for the demonstration of bioequivalence. Some general reflections on the proposals can be found below.

- Simulation of concentrations in target compartments is of great interest however based on the current knowledge this is more like a learning exercise than an exercise that can support a regulatory submission.
- A model based FIM dose selection is an area of great scientific interest and welcomed in support of regulatory dossiers.
- PK/PD modelling can be supportive but is not currently adequate as a stand-alone analysis for bio-similarity, if there is a need for clinical comparability data based on PD surrogates or clinical endpoints.
- There is a very specific regulatory position on biowaivers and bioequivalence. Unless model based methods are qualified to support such uses it will be difficult to accept M&S in this context.

Methods discussed in 2015



POP-PK: Population Pharmacokinetic Modelling
POP-PK/PD: Population Pharmacokinetic/Pharmacodynamic Modelling
PBPK: Physiologically Based Pharmacokinetic Modelling
Other: Mechanistic Static Model, Model averaging, Dose-Response, PK-Efficacy Model

Mapping 2015 Activity report to the 2015 work plan

In general terms very good progress was achieved in the areas identified. Some activities are still ongoing (i.e. extrapolation, PBPK) due to the complexity of the issue or due to the fact that they have long term deliverables (e.g. assessors guides and harmonisation of regulatory requirements on M&S).

Guideline on extrapolation. In collaboration with the Extrapolation Working Group. An overarching concept paper has been written by the Extrapolation Working Group. PKPD modelling is one of the most common tools utilised in extrapolation across populations and therefore has high regulatory impact requiring clear guidance on regulatory standards for methodology and documentation. In addition the MSWG will be closely involved in the update of ICH E11.	Comments provided in draft guideline. Continues in 2016.
Assessor Guide on dose finding/selection in children. This internal overarching document will provide some practical recommendations on how to perform dose finding/selection in children. End date: December 2015. It is envisaged that the assessor guide will inform future regulatory guidance documents. Specific methodological topics on extrapolation and dose finding in children will be addressed in a Q&A document. This will be updated regularly to reflect the evolving regulatory views and the scientific advancements in the field. As with the assessor guide this Q&A document will initially be internal but it is envisaged to be made public.	First overarching document available in form of a book chapter under submission. Continues in 2016.
Guideline on development and reporting of physiologically based pharmacokinetic (PBPK) models. In collaboration with PKWP. Because of their mechanistic basis, these models have great value to predict drug-drug interactions, PK in the paediatric population and impact of organ impairment and aging. Given their complexity, however, careful consideration of an appropriate qualification of models, particularly as applied to individual molecules is needed. Also, as the generic models included in commercially available software are continually evolving, there is a unique challenge of continuous system validation. Draft guideline to be released for consultation 2H 2015.	Comments provided in draft guideline. Continues in 2016.

Harmonisation of regulatory requirements for M&S. The MSWG will work on establishing internal regulatory standards for conduct, evaluation and reporting of M&S approaches in support of regulatory submissions. It is envisaged that these standards will be the basis for future regulatory guidelines on M&S.	This is an activity with long term deliverables. Continues in 2016.
Contribution to replacement of the **Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products (CPMP/EWP/2655/99)**. In collaboration with IDWP.	Comments provided in draft guideline. Participation in the EMA workshop on PK/PD of antibiotics. Continues in 2016.
Contribution to the concept paper on the **Addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections in the paediatric population.** In collaboration with IDWP.	Contribution deferred for 2016.
Work towards an update of the CHMP assessment report templates to focus in the evaluation of dose-exposure-response relationship. This is an action arising from the dose finding workshop. The characterisation of dose-exposure-response relationship should be an integral part of drug development. The update on the CHMP templates will reinforce the importance and facilitate the evaluation of dose-exposure-response relationships at the stage of MAA, to support B/R decisions and to inform the Risk Management Plan (RMP).	First draft with MSWG contribution on CHMP D80 AR Clinical Guidance is circulated internally. Publications in scientific journals/book chapters on DER are under review or in drafting stage. Continues in 2016.
Activities with external parties	Active representation in international meetings (list not exhaustive): • Europe DIA 2015, Paris, FR • PAGE 2015, Crete, GR • ISSX European Meeting 2015, Glasgow, Scotland • Marbach International DDI workshop 2015, DE • ACOP 2015, Crystal City, VA • Annual joint DIA/EFGCP/EMA conference 2015, London, UK • IATDMCT 2015, Rotterdam, NL • EFPSI meeting 2015, Braine l'Alleud

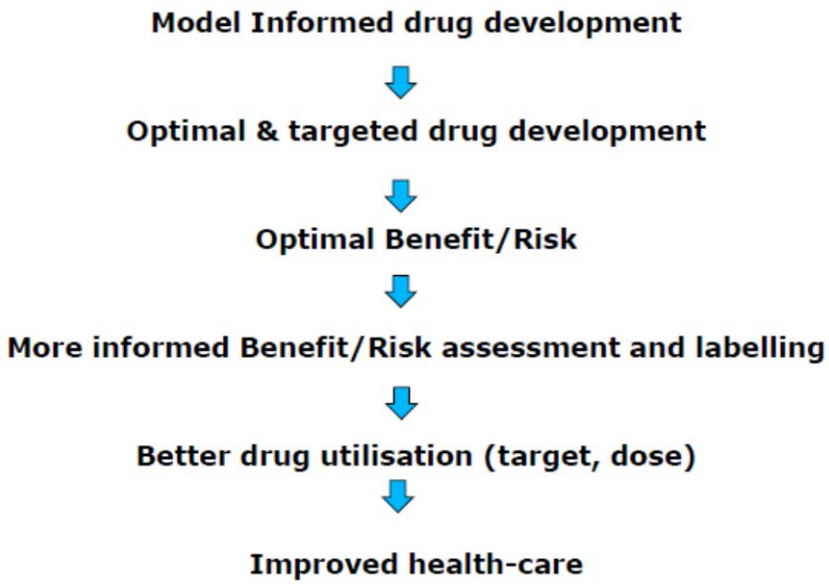
	Communication with external Stakeholders: • With EFPIA on MID3 good practices and extrapolation framework • With DDMore IMI project • With FDA, PMDA and Health Canada on Extrapolation • Collaboration with FDA on PBPK

Objectives of MSWG

- To enhance the collective competence and capacity to provide advice on and assessment of modelling and simulation in marketing authorisation applications and PIPs, reducing uncertainty in benefit risk decisions and improving product labelling.
- To advance early communication and “support innovation” with industry and academia in areas like first in man, dose finding, study optimisation, disease progression and extrapolation where modelling and simulation can play an important role.
- To develop and communicate standards for the design, conduct, analysis and reporting of modelling and simulation according to the level of regulatory impact, with particular emphasis on those of high regulatory impact such as extrapolation to paediatric and elderly populations.
- To increase awareness and acceptance of modelling and simulation approaches across the European national authorities.

Scientific vision / long term workplan

To establish M&S as a platform for a systematic quantitative approach to underpin and explain the underlying scientific rationale for the selected pathways, target mechanisms, molecule attributes, experimental designs, dose regimes, and patient populations investigated. The systematic integration of compound specific and mechanism and disease area relevant information should help to create a comprehensive, complete, and contemporary body of evidence for well-informed decision both for the drug developer, for the regulator, and the prescriber. This body of evidence will extend beyond product specific contexts and will evolve in systems knowledge, which will be accessible (publication of models & non-competitive raw data) to researchers and drug developers. It is also envisaged that integrated data analysis encompassing all stages of development, based on modelling and simulations, will be requested/conducted routinely during MAA assessment, with the objective to inform the SmPC and optimise the RMP. As a result of all the above activities, which are central to the role of MSWG, the patient will receive optimal pharmacotherapy.



Current composition

Ine Skottheim Rusten (chair, NO), Flora Musuamba Tshinanu (Vice Chair, BE) , Frederike Lentz (DE), Anna Nordmark (SE), Gérard Pons (FR), Norbert Benda (DE), Joe Standing (UK), Johannes Taminiau (NL), Wei Zhao (FR), Susan Cole (UK), Valeria Gigante (IT).

Members have advanced knowledge of modelling and simulation methodology and hands on experience in computational techniques, such as population PK, PK/PD, PBPK (physiologically based pharmacokinetic) and complex statistical M&S.

Tomas Salmonson and Robert Hemmings act as observers to the MSWG, with Robert Hemmings providing the continuity to the SAWP. Efthymios Manolis, Cecile Ollivier attend from the EMA.