9 April 2015
EMA/91752/2015

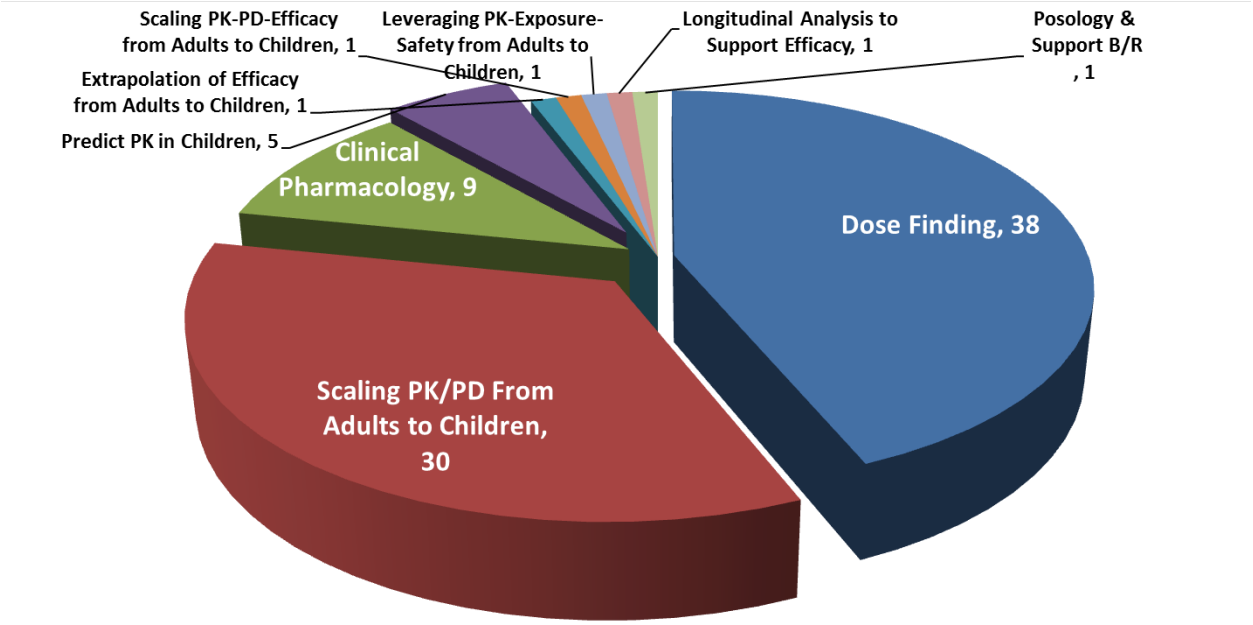
2014 Activity report of the Modelling and simulation working group (MSWG)

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 2014 to December 2014, 85 procedures were referred to the MSWG with the vast majority from SAWP (56 including 3 Qualifications), 24 from PDCO, 1 from CHMP and 4 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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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 Because dose finding is traditionally considered of low/medium regulatory impact as it is superseded by pivotal efficacy and safety data (although high risk for the company), these reviews could be considered as "enabling innovation".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-response relationship is often a concern during the assessment of new medicines, and could result in 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. 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)

Scaling PK/PD from adults to children

Models with the inclusion of covariates to account for growth and maturation or any other characteristics are used to extent and characterise the PK/PD relationship from adults to other 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. Less common is the use of methods (PK/PD efficacy models, Bayesian & statistical models, exposure safety analyses) which make direct inferences about efficacy/safety in children based on adult data, and limited data in children.

Clinical Pharmacology

Regarded as uncontroversial and is welcomed. Specific reference is made in the EMA DDI guideline.

Predict PK in children

This refers to the use of PBPK models together with in vitro, in vivo data on ADME to predict the PK profile in children. These methods are often used together with population PK analyses in an effort to reduce-highlight uncertainties when scaling from adults to children.

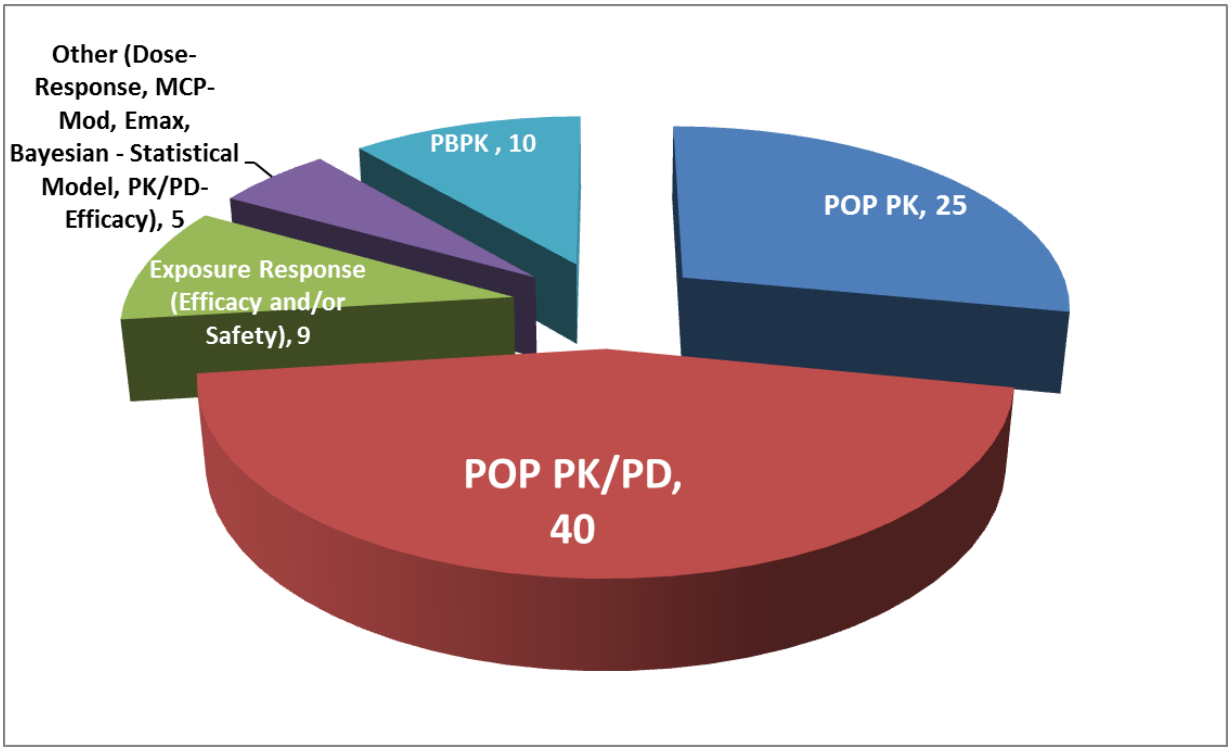
Posology

The elucidation of Dose-Exposure-Response relationship based on the totality of data with the use of models and investigation of different what if scenarios through simulations could lead to optimal dose recommendations and B/R ratio even if the final dose regimen is different to the one tested in Phase III. The specific category refers to cases where dose recommendations on the basis of M&S were proposed based on the totality of data available at the stage of MAA.

Longitudinal analysis to support efficacy

Modelling has been identified as a key method to analyse longitudinal data, for example in support of disease modifying claims.

Methods discussed in 2014



POP-PK (/PD): Population Pharmacokinetic (-Pharmacodynamic) Modelling
PBPK: Physiologically Based Pharmacokinetic Modelling
Other: These methods are based on statistical rather than pharmacological assumptions, i.e. Dose-Response models, MCP-Mod, Emax model, Bayesian & other Statistical models, PK/PD-efficacy models.

Mapping 2014 Activity report to the 2014 work plan

In general terms very good progress was achieved in the areas identified- especially considering the fact that the planning assumed that there will be an upgrade of the group to working party status with 2 planned face to face meetings. Some activities are still ongoing (i.e. extrapolation) due to the complexity of the issue. Others (i.e. guidance for regulatory submissions and guidance for assessors) were referred to 2015 due to work load and limited resources.

Guideline on extrapolation (2H2014). In collaboration with the Extrapolation Working Group. An overarching concept paper has been written by the Extrapolation Working Group. PK/PD 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	Ongoing

methodology and documentation.	
Concept paper on development and reporting of physiologically based pharmacokinetic (PBPK) models (2H2014). 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.	Complete. Refer to 2015 work plan regarding the expected contribution on the guideline.
Concept Paper on revision of the Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products (1H2014). This is an IDWP guided activity, MSWG contributed with comments on the M&S methodology.	Complete. Refer to 2015 work plan regarding the expected contribution on the points to consider.
Guidance (could be a Q&A document) on how to best use and incorporate modelling and simulation in regulatory submissions (2H2014). This was identified as a barrier to companies explaining the modelling basis of their drug development decisions in the submitted dossiers. As this type of modelling integrates data across studies and potentially from preclinical to clinical studies, including pharmacological and clinical endpoints, it can be an invaluable "chain of evidence" to reduce uncertainty in benefit/risk decisions and inform and strengthen the RMP.	Project was deferred to 2015/2016.
M&S Template for assessors. This will help streamline the regulatory approach on M&S.	Project was deferred to 2015/2016.
Workshops	Dose finding workshop successfully organised
Activities with external parties	Active representation in international meetings: • FDA open meeting on Application of Physiologically-based Pharmacokinetic (PBPK) Modeling to Support Dose Selection. FDA, 10 March, 2014 • DIA/FDA Statistics Forum 2014 scheduled

	Bethesda, MD, 7-9 April, 2014 • 7th Noordwijkerhout symposium on Pharmacokinetics, Pharmacodynamics and Systems Pharmacology. NH Conference Centre Leeuwenhorst, 23- 25 April, 2014 • M-CERSI/FDA/ACCPs "Innovative Approaches to Pediatric Drug Development and Pediatric Medical Countermeasures: A Role for Physiologically-Based PK?" FDA, 5 May, 2014 • PAGE meeting, Alicante, 10-13 June, 2014 • Ministerial Industry Strategy Group (MISG) Forum on Physiologically-based Pharmacokinetic (PBPK) Modelling and Simulation. MHRA, London, 30 June, 2014 • ACOP meeting, Las Vegas, Nevada, 12 – 15 October, 2014 • PKUK meeting, Bath, 5 - 7 November 2014 Communication with external Stakeholders: • With EFPIA on MID3 good practices and extrapolation framework • With DDMore IMI project • Collaboration with EFPIA on the organisation of the dose finding workshop. • Consultation with FDA and PMDA on the contents of the dose finding workshop and key messages. • 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.

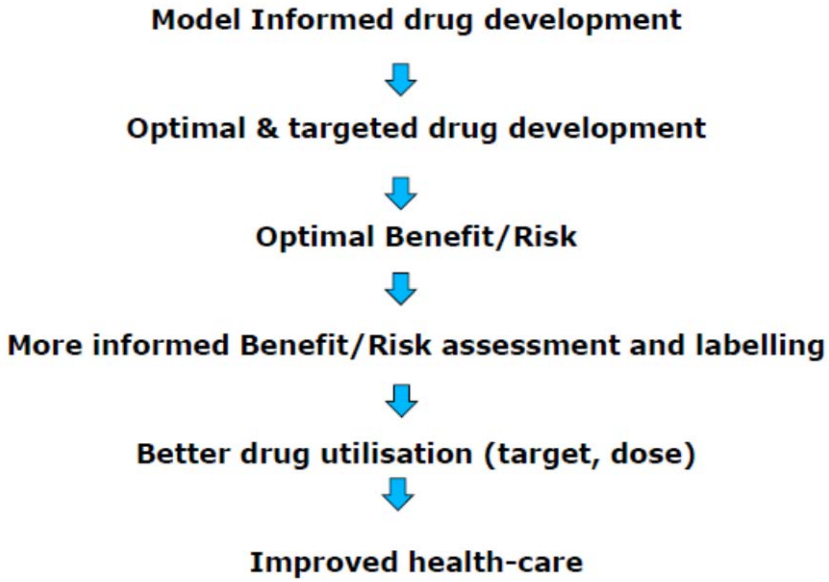
- To advance early communication and "support innovation" with industry and academia in areas like first in man, dose finding, study optimisation, disease progression and extrapolation where modelling and simulation can play an important role.

- 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

Terry Shepard (chair, UK), Ine Skottheim Rusten (vice chair, NO), Sofia Friberg Hietala (SE), María Jesús Garrido (ES), Frederike Lentz (DE), Flora Musuamba Tshinanu (BE, UK) , Anna Nordmark (SE), Gérard Pons (FR), Norbert Benda (DE), Joe Standing (UK), Johannes Taminiau (NL), Petra Schmitt (PEI), Wei Zhao (FR), Anna Karin Hamberg (SE), 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.