# 2016 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 2016 to December 2016, 105 product related procedures were referred to the MSWG with 41 from PDCO, 62 from SAWP, 2 from CHMP and 7 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.
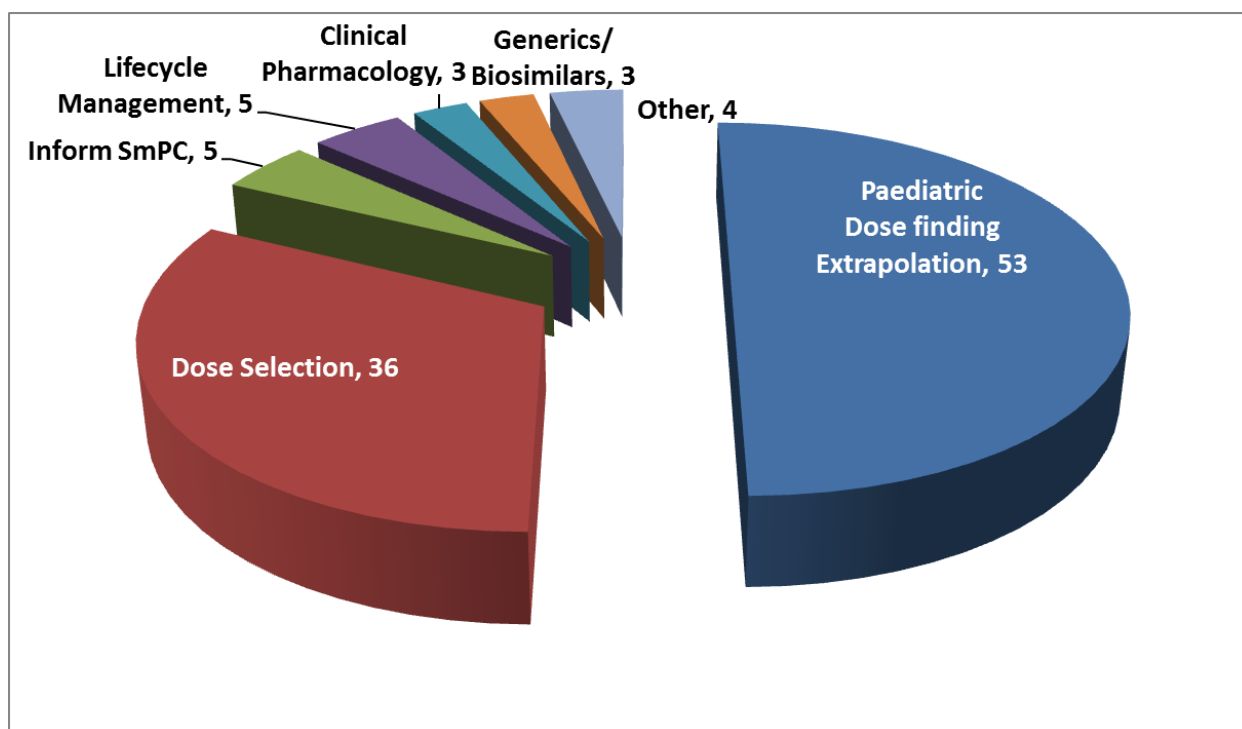
Paediatric Dose Finding/Extrapolation

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 age 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 Selection

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 Because dose finding is traditionally considered of low/medium regulatory impact as it is superseded by pivotal efficacy and safety data (although high risk for the company), these reviews could be considered as "enabling innovation".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.

Inform SmPC

This refers to the use of dose exposure response analyses and/or PK/PD modelling to support SmPC claims mainly on posology section.

Lifecycle Management

M&S is emerging as a method supporting the life cycle management of medicinal products, e.g. new dose regimens, new formulations, route of administrations and the design of post approval studies. The characterisation of exposure response relationship pre-marketing enables the use of M&S to support post-approval changes often without the need for dedicated clinical studies.

Generics & biosimilars

The use of modelling techniques in the generic and biosimilar space is controversial from a regulatory perspective. Nevertheless exposure response analyses were submitted to justify bioequivalence margins, and this is an area where M&S could add value.

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.

Other

M&S was proposed in submissions as a tool to bridge efficacy data to a new route of administration, from non-pregnant to pregnant women, to inform the need for therapeutic drug monitoring (TDM) as part of drug development and in the SmPC, to justify a biowaiver of a new oral formulation and to quantify the predictive properties of biomarkers.

Some general reflections on the proposals can be found below.

- There is currently 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.

- Using M&S to support extrapolation between different populations is encouraged however more experience is needed with the use of models to predict PK/PD in pregnant women.

- M&S can be used to identify sources of variability that affect PK/PD and efficacy and safety. In the case the unexplained variability is still large and has clinical consequences therapeutic drug monitoring (TDM) can be considered.

Methods discussed in 2016
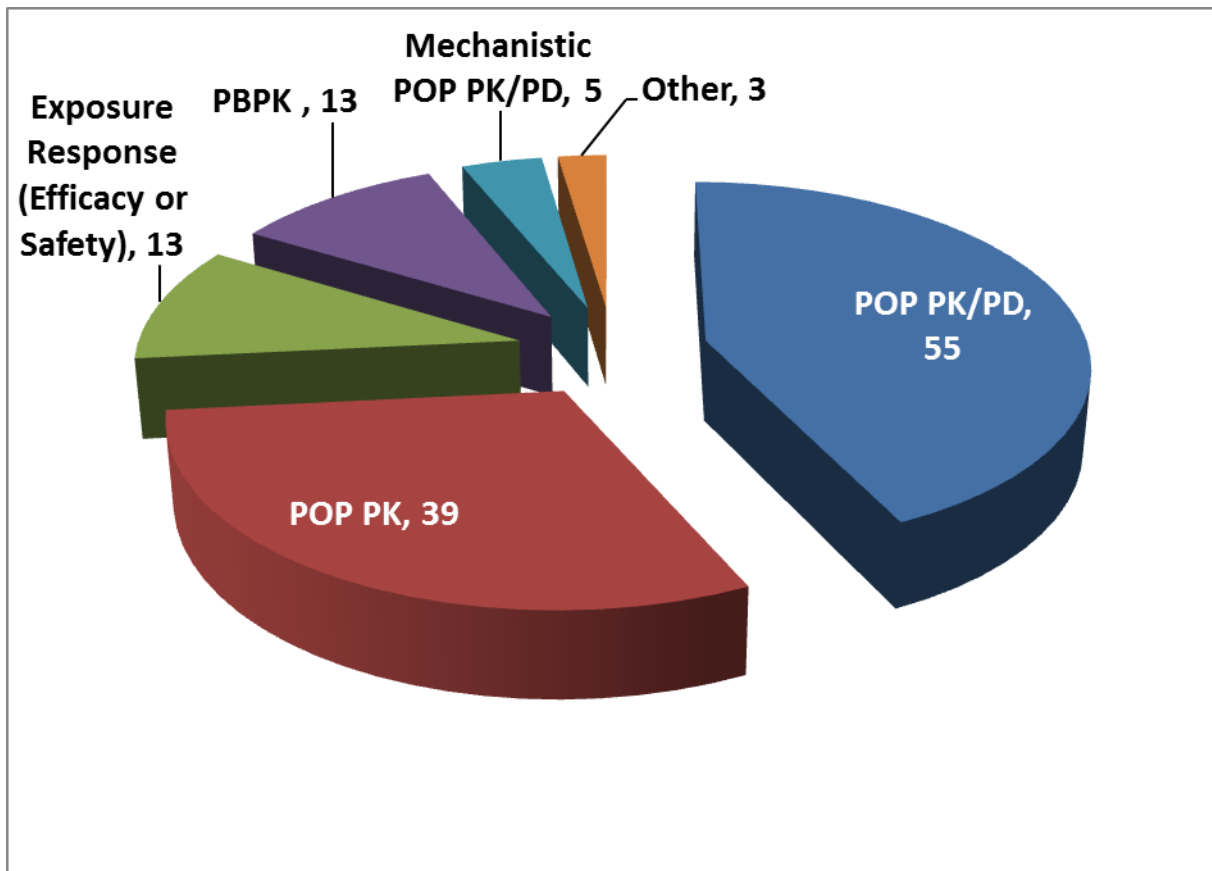
POP PK: Population Pharmacokinetic Modelling
POP PK/PD: Population Pharmacokinetic/Pharmacodynamic Modelling
PBPK: Physiologically Based Pharmacokinetic Modelling
Exposure Response: Cross sectional exposure response analyses
Other: Statistical Modelling, POP PK/PD-Efficacy Modelling

Mapping 2016 Activity report to the 2016 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).

EU guidelines	
Guideline on development and reporting of physiologically based pharmacokinetic (PBPK) models	Draft Guideline out for public consultation. PBPK Workshop held on 21 Nov 2016.
Reflection paper on extrapolation of efficacy and safety in paediatric medicine development	Draft guideline released for public consultation. Extrapolation Workshop held on 17-18 May 2016. Final guideline to be released 2017.
Paediatric Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections	Comments provided on Concept Paper (CP). Further contribution expected in the guidance document in 2017. Draft to be released for public consultation Q2 2017.
Note for guidance on the Role of pharmacokinetics in the development of medicinal products in the paediatric population	Comments provided on CP. Further comments on the note for guidance will be provided in 2017.
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. Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products was adopted by CHMP on 27 July 2016.
ICH guidelines	
E11(R1) Clinical investigation of medicinal products in the paediatric population	Input from MSWG provided. ICH E11 GL under public consultation.
ICH E14 working group on collaborative data gathering and analyses	Input from MSWG provided. Activity continues in 2017.
Assessor Guides	
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 benefit /risk (B/R) decisions	The CHMP D80 AR Clinical Guidance is updated based on the MSWG comments. Publications in scientific journals/book chapters on DER are under review or in drafting stage. Continues in 2017.

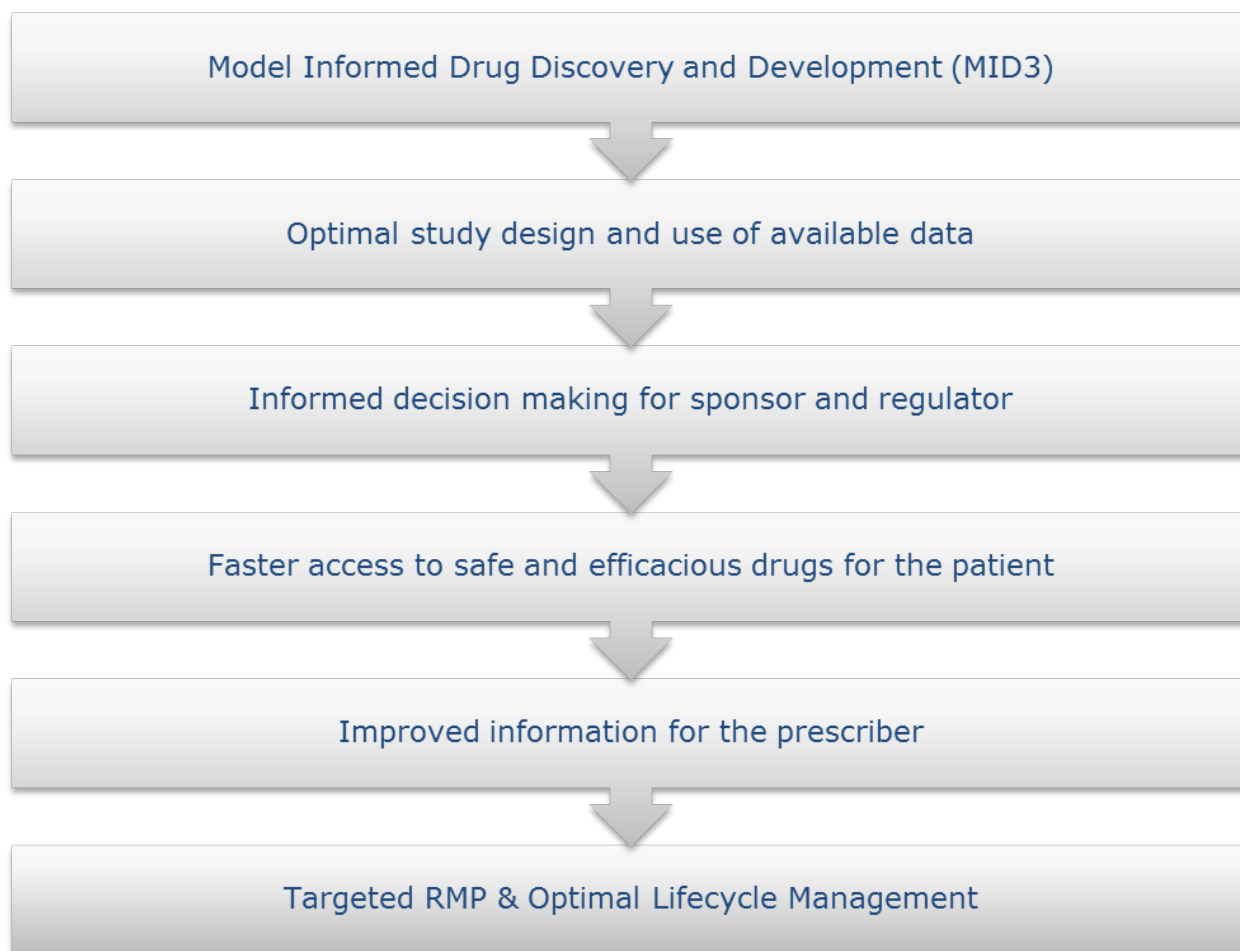|	
and to inform the SmPC and the Risk Management Plan (RMP).	
Assessor Guide on dose finding/selection in children. This internal overarching document will provide some practical recommendations on how to perform dose finding/selection in children. It is envisaged that the assessor guide will inform 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 in Fundamentals of Pediatric Drug Dosing. Editors: Mahmood, Iftekhar, Burckart, Gilbert (Eds.). Scaling Dose-Exposure-Response from Adults to Children Rusten, Ine Skottheim (et al.) 2016. Continues in 2017.
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 2017.
Activities with external parties	
International regulatory cluster on M&S with participation of EMA, US-FDA, MHLW/PMDA and Health Canada	4 Cluster TCs organised in 2016
Active representation in international meetings	List not exhaustive: • PAGE meeting • WCOP meeting • ACOP meeting • Workshop on identifying opportunities for 'big data' in medicines development and regulatory science • First Conference of the European Association of Systems Medicine • DG-RTD Health Directorate/EMA Workshop • 'Systems medicine: Regulatory challenges and research & innovation solutions'
Communication with external Stakeholders:	Interactions with the following groups took place in 2016: • With EFPIA on MID3 good practices and extrapolation framework • With DDMore IMI project

Workshops/trainings	
PBPK Workshop	Held 21 Nov 2016
Extrapolation Workshop	Held 17-18 May 2016
Trainings on different modelling and simulation platforms	NONMEM, GastroPlus, PKSIM

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 and in a shorter timeframe.

Model Informed Drug Discovery and Development (MID3)

Optimal study design and use of available data

Informed decision making for sponsor and regulator

Faster access to safe and efficacious drugs for the patient

Improved information for the prescriber

Targeted RMP & Optimal Lifecycle Management

Current composition

Ine Skottheim Rusten (chair, NO), Flora Musuamba Tshinanu (Vice Chair, BE) , Norbert Benda (DE), Jacob Brogren (SE), Susan Cole (UK), Aristeidis Dokoumetzidis (GR), Valeria Gigante (IT), Kristin Karlsson (SE), Frederike Lentz (DE), Anna Nordmark (SE), Justin Pittaway-Hay (UK), Gérard Pons (FR), Francesca Serone (IT), Joseph Standing (UK), Johannes Taminiau (NL), Juha Vakkilainen (FI), Michiel van den Heuvel (NL), Gaby Wangorsch (DE), Wei Zhao (FR)

Members have advanced knowledge of modelling and simulation methodology and/or 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 attends from the EMA.