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2013 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 its establishment in January to December 2013, **59 procedures were referred to the MSWG with the vast majority from SAWP (51), 4 from PDCO, 1 from CHMP and 3 Qualification Procedures.** A breakdown of the scope of questions addressed by M&S is shown in the pie chart below:

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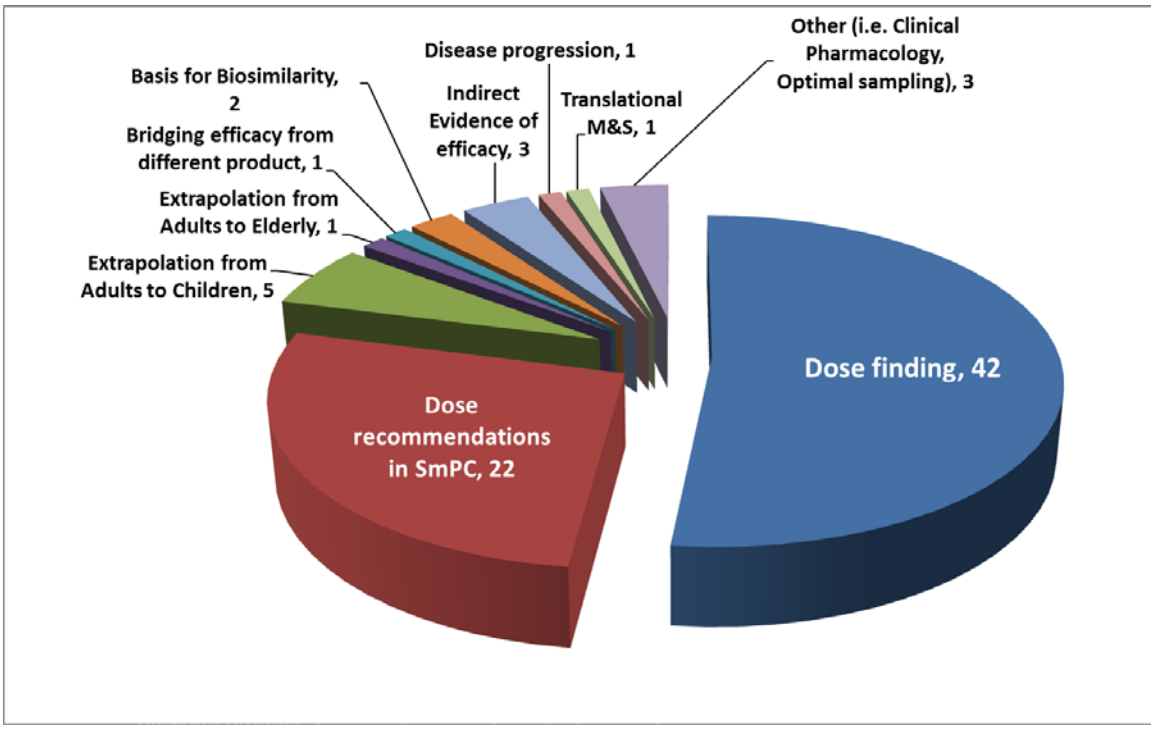


Specific examples where the MSWG advice have added value to the assessment of the committees and working parties as evidenced by the final outcomes of these procedures are summarised in the table below.

Procedure	Question to MSWG	Contribution to Final Outcome	Impact
Product 1 Biosimilar Mab (SAWP)	Does the MSWG agree that the proposed PK/PD modelling approach, if successful, is sufficient to provide sufficient **evidence of clinical** similarity?	*Text added in the final advice letter:* The evaluation of PD Data and PK/PD modelling analyses are endorsed and convincing data can be considered as a supportive part within the overall biosimilar development program. Technical comments were addressed on the **PK/PD modelling analyses.**	*High Regulatory* *High for Sponsor*
Product 2 MAA based on limited clinical data (SAWP)	Does the MSWG agree to the rationale for **dosing** and the proposed dosing regimen?	*Text added in the final advice letter:* The modelling approach is **generally supported**. However, as very limited details and no model validation results have been provided, the validity of the simulation results guiding dose selection cannot be evaluated. Included a list of points that the Company may wish to consider in future model refinement including: translational models for incorporating the important animal data; consideration of dose-proportionality; impact of covariates; **extensive documentation will be necessary at time of MAA, since clinical data will be limited and modelling will play an important role in assessment.**	*High Regulatory (limited clinical development)* *High for Sponsor (limited clinical development)*

Product 3 (SAWP)	Does the MSWG agree with the proposed M&S approach to support **dose finding?**	*Text added in the final advice letter:* Based on the Ph1b results the proposed dose **could be acceptable**. However the use of modelling in the dose finding is **not considered optimal** because: a) the model is based on healthy volunteer data, and b) the **external validity** of the model is questionable (model did not converge with Ph1b data in patients). The sponsor is encouraged to **rebuild the model based on the totality of data** available taking into account the differences between HV and patient population. **This will strengthen the dose finding and will further support the Proof of Concept and the rationale for 1 pivotal trial**.	*Medium Regulatory High for Sponsor*
Product 4 (SAWP)	Does the MSWG agree with the proposed M&S approach to support **extrapolation of PK/PD (and efficacy) from adults to elderly?**	*Text added in the final advice letter:* Given the conflicting information on the impact of renal impairment on PK, data derived from the pivotal efficacy and safety trial are viewed as highly useful to add to the understanding of intrinsic factors important for PK and recommended posology. Applicant should include **informative blood sampling time points** (optimal sampling strategy could be employed), quantify plasma protein binding and include a reliable measure of renal function.	*High Regulatory High for Sponsor*
Product 5 Mab 1 (CHMP)	Does the MSWG agree with the proposed modelling and simulation approach for **assessing different dose regimen post marketing and include this information in SmPC section 5.2?**	The MSWG **did not agree** that the model is developed and validated to a sufficient standard to allow fully reliable inferences from model-derived simulations. However MSWG **understood that the clinical context provides reassurance for that alternative dosing.** An **alternative wording to capture the considerations above was proposed** by MSWG and adopted by CHMP for SmPC section 5.2.	*High Regulatory High for Sponsor*

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

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. As modelling approaches are more efficient, they are also more likely to result in optimal dose selection.

Dose recommendations in SmPC

To date another quarter of the questions referred to the MSWG addressed questions related to M&S in support of dose recommendations in the SmPC. These have typically been of medium or high regulatory impact. Examples include

- M&S in addition to standard inferential testing with the objective to fine tune dose recommendations- medium impact
- M&S to support bridging/extrapolation from literature or in house data using limited clinical data in the target population (PK, PD, efficacy, safety) - high impact
- Simulations to support dose recommendations that have not been tested in the clinic – high impact

Extrapolation

Models with the inclusion of covariates to account for growth and maturation or any other characteristics are used to extent and characterise the Dose-Exposure-PD-Clinical Response relationship from adults to other groups.

Although M&S is the tool of choice to support extrapolation, most often the extrapolation assumptions are based on clinical practice and basic pharmacology principles. The EMA concept paper opens the discussion for a more quantitative framework.

DDI /Clinical Pharmacology

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

Extrapolation from preclinical models to human (translational Modelling and Simulation)

This is an area of great research as witnessed by the qualification of several translational biomarkers. Also in the Guideline on Strategies To Identify And Mitigate Risks For First-In Human Clinical Trials With Investigational Medicinal Products a PK/PD modelling approach is recommended in support of MABEL.

Longitudinal analysis to characterise disease progression

Modelling has been identified as a key method to analyse longitudinal data, for example in support of disease modifying claims. The recent qualification opinion on Alzheimer's disease highlights the utility of modelling.

Indirect Evidence of Efficacy

In the Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections it is highlighted that alternative approaches are needed to accumulate evidence to support a specific endorsement for treatment of MDR pathogens that are susceptible to few licensed

antibacterial agents. These approaches rely heavily on PK/PD data analysis and modelling & simulation is a tool of choice for this analysis.

Biosimilar

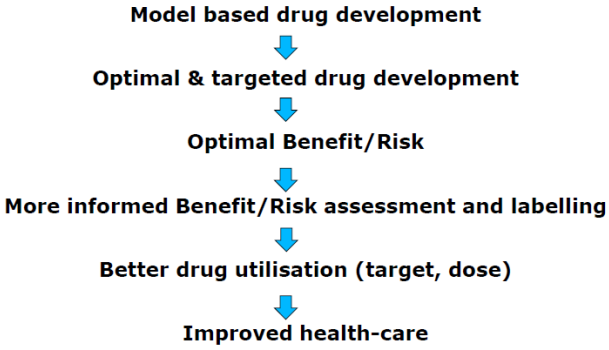
In principle it can be accepted that PK/PD, dose-response or longitudinal analyses are more sensitive methods than clinical outcome analysis at a single fixed timepoint to detect differences between originator and bio-similar. The use of Modelling and Simulation to support bio-similarity was the subject of previous scientific advice and a qualification advice procedure.

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), Jacob Brogren (vice chair, SE), María Jesús Garrido (ES), Frederike Lentz (DE), Flora Musuamba Tshinanu (BE, UK) , Anna Nordmark (SE), Gérard Pons (FR), Ine Skottheim Rusten (NO), Johannes Taminiau (NL), Nadine Eva Van Egmond (NL), Norbert Benda (DE), Joe Standing (UK), Ridha Belaiba (FR). 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 Rob Hemmings act as observers to the MSWG, with Rob providing the continuity to the SAWP. Petra Schmitt (Expert in Biologics, PEI) has recently joined as an observer. Efthymios Manolis, Spiros Vamvakas attend from EMA.