Regulatory pharmacometrics in the EU in practice, and the role of the Modelling and Simulation Working Group

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MEDICAL PRODUCTS AGENCY

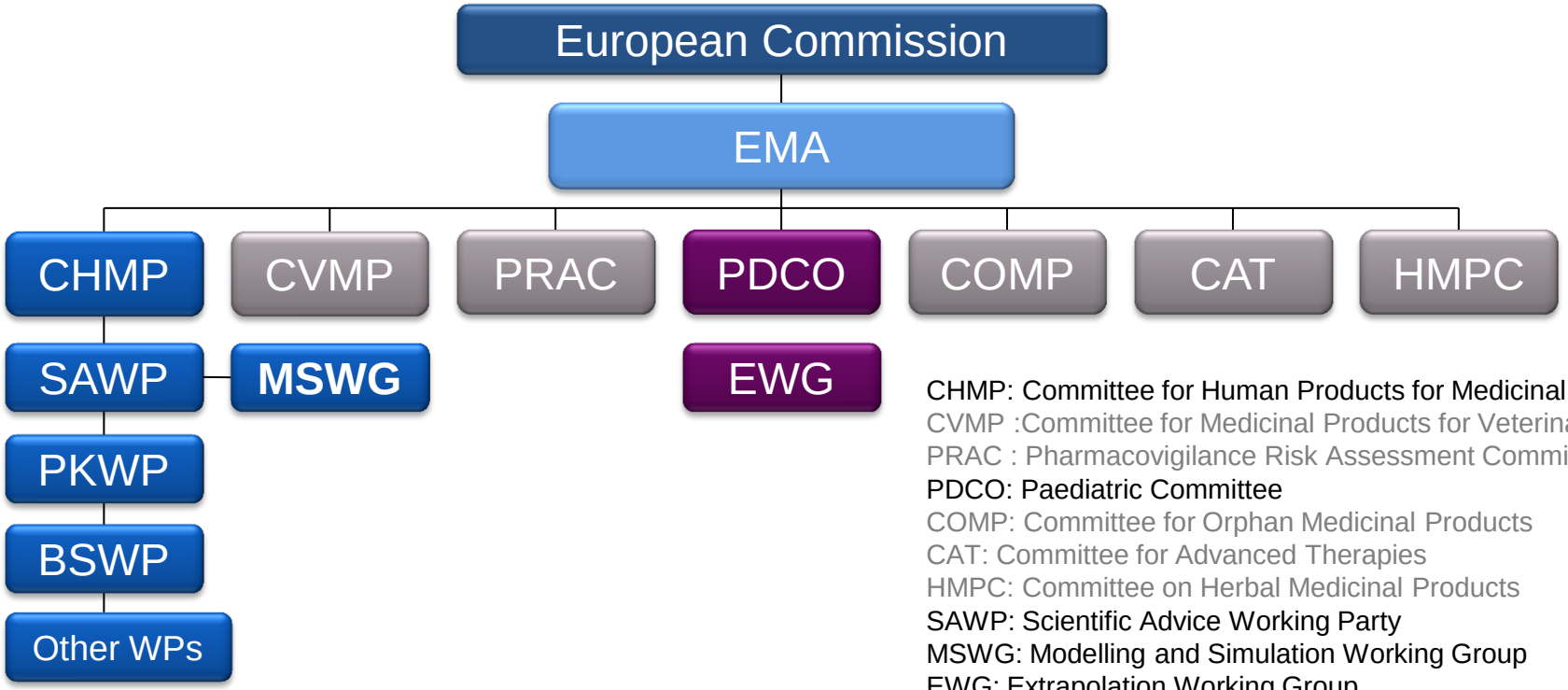
Disclaimer

The views expressed in this presentation are those of the speaker, and are not necessarily those of MPA or EMA.

Outline

- Organisation of EMA and National Competent Agencies
- What is the role the Modelling and Simulation Working Group (MSWG)?
- Who does the assessment of pharmacometric analyses within Market Authorisation Applications (MAAs)?
- Examples
  - Central Scientific Advice (SAWP)
  - Approval of a new drug
  - New indication, paediatrics
- Take home messages
- References for good reporting standards

EMA framework



CHMP: Committee for Human Products for Medicinal Use
CVMP :Committee for Medicinal Products for Veterinary Use
PRAC : Pharmacovigilance Risk Assessment Committee
PDCO: Paediatric Committee
COMP: Committee for Orphan Medicinal Products
CAT: Committee for Advanced Therapies
HMPC: Committee on Herbal Medicinal Products
SAWP: Scientific Advice Working Party
MSWG: Modelling and Simulation Working Group
EWG: Extrapolation Working Group
BSWP: Biostatistics Working Party
PKWP: PK Working Party

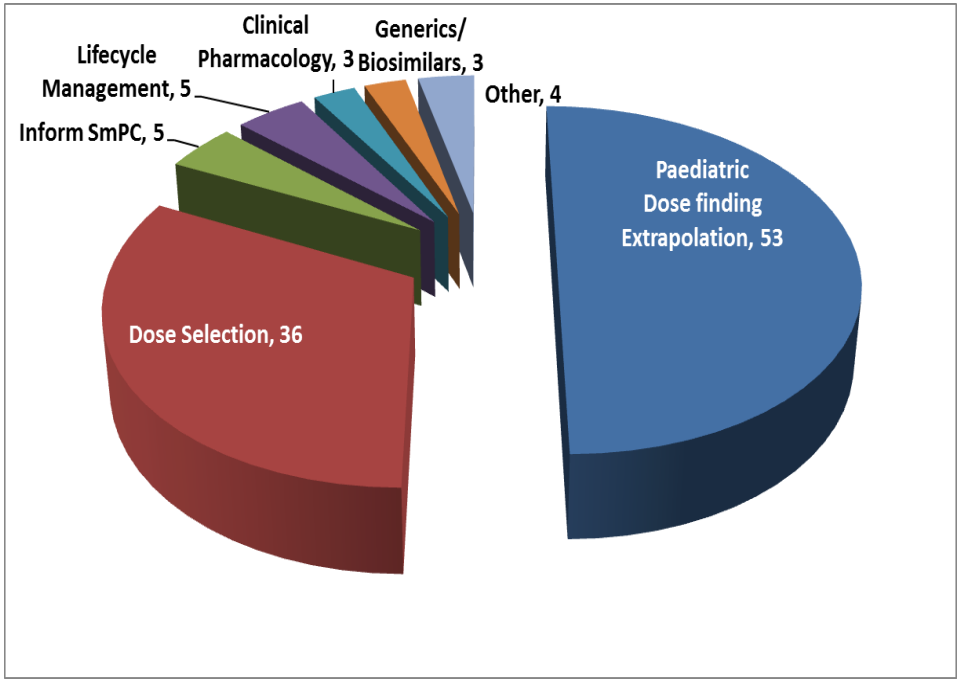
What is the role of MSWG?

- Provide support for
  - Scientific Advice Working Party
  - Paediatric Committee (Paediatric Investigation Plans)
  - Referrals from CHMP
- Strategic work within EMA framework (guidelines etc)
- Act as a network for pharmacometric assessors
  - Support between national agencies
  - Harmonization of pharmacometric assessments

- Assessment of M&S analyses within Market Authorisation Applications (MAA) are performed at the National Competent Agencies

MSWG 2016 Activity Report

- **105 product related procedures**
  - **41 from PDCO,**
  - **62 from SAWP,**
  - **2 from CHMP**
  - **7 Guidelines**
- A breakdown of the **scope** of questions addressed by M&S is shown in the pie chart



Courtesy of Efthymios Manolis

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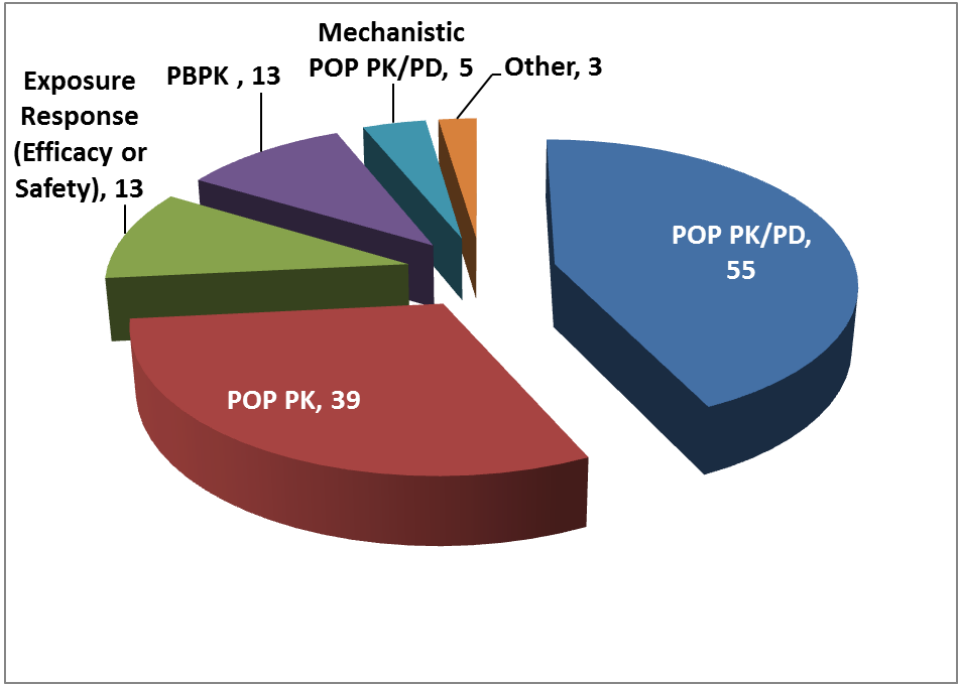

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Who are in the Modelling and Simulation Working Group?

Modellers from regulatory agencies and academia* with advanced knowledge of modelling and simulation methodology and/or hands on experience in computational techniques, such as population PK, PK/PD, PBPK and complex statistical M&S

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

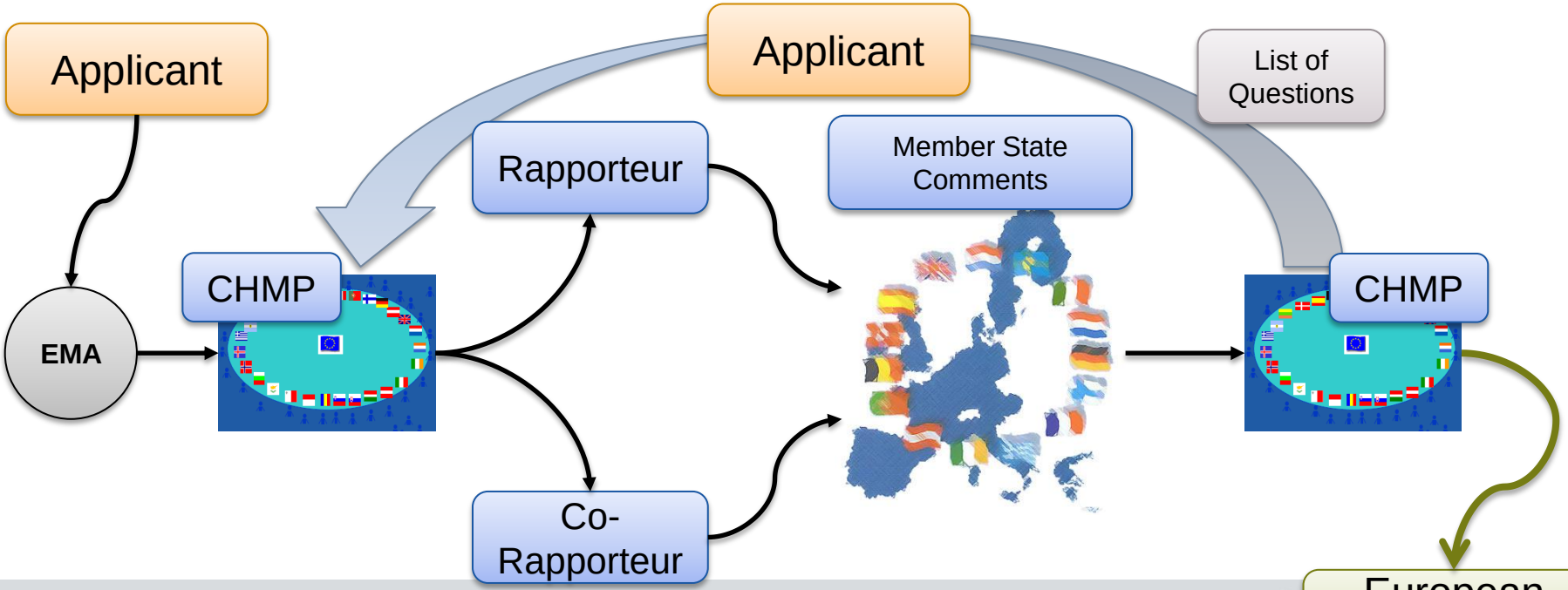
EMA

- Efthymios Manolis

CHMP/SAWP

- Tomas Salmonson
- Robert Hemmings

Who does the assessment of pharmacometric analyses within Market Authorisation Applications in EU?



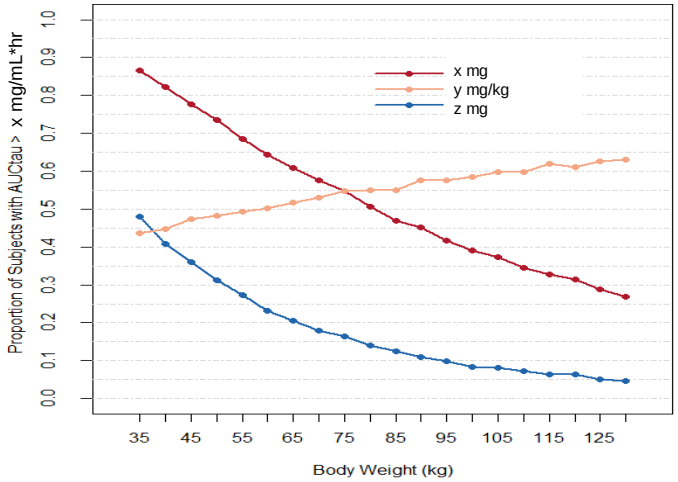
Areas where pharmacometric expertise is commonly needed

- Central scientific advice (SAWP)
- Description of PK in special populations (in target population)
- Dose selection
  - We encourage pharmacometric analyses of phase 2 data (dose-ranging) to support dose selection
- Paediatric indications
  - Population PK analyses are pivotal when extrapolation from adults is used for efficacy (and safety)
- PBPK to inform on drug-drug interactions (DDI)

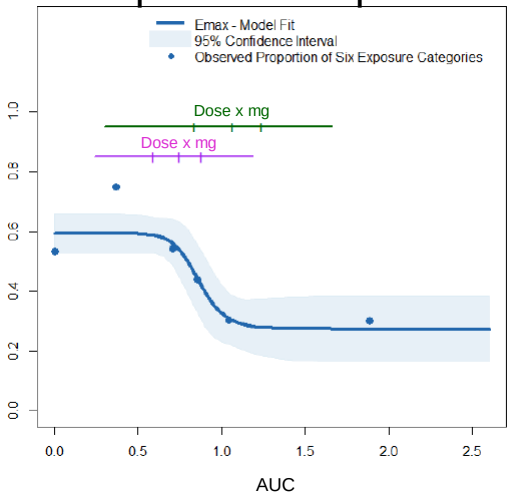
Example: Scientific Advice

- "*Does the CHMP agree with the scientific basis and Sponsor rationale for the dose selection strategy for the proposed Phase III studies and that the dose selected is appropriate for the Phase III program?*"

PK



Exposure-Response



If it is mentioned in the question that M&S methodology is used, it is more likely that M&S experts are included in the team of advisers.

Example: Scientific Advice

"*Does the CHMP concur with the Sponsor's opinion that the proposed population PK and PK/PD plan, when executed, adequately supports the proposed Phase III clinical development program and a marketing authorization application in the sought indication?*"

Make sure to provide sufficient background information to receive an informed advice

Example: PK in a new drug, special populations

Other concern

“Several issues need to be clarified to adequately substantiate the impact of intrinsic factors on PK:

a. *Clinical relevance of the covariate model: the clinical relevance of the covariates in the final PPK model appears to be very marginal as no significant reduction of the inter-subjects variability is observed in the final model comparatively to the base model. Please discuss if this is due to inter-occasion variability not accounted for.*

Overall, the applicant should further describe impact of intrinsic factors conciliating both data from PPK and from formal studies.”

Please provide scientific rational for, for example, apparent model miss-fits or and inclusion small covariate effects.

Example: Dose selection for a new drug

Other concern

“As the exposure-response analyses and subsequent simulations to assess efficacy, indicate that the proposed dose might be sub-optimal for some patients it is crucial that the proposed dose and dosing regimen are well justified. In addition, alternative dosing strategies such as dose escalation or dosing regimen should be discussed.”

The dose selection is no longer viewed as purely the “sponsor’s risk” by CHMP, hence the posology can be questioned

Example: New indication, paediatrics

Major objection

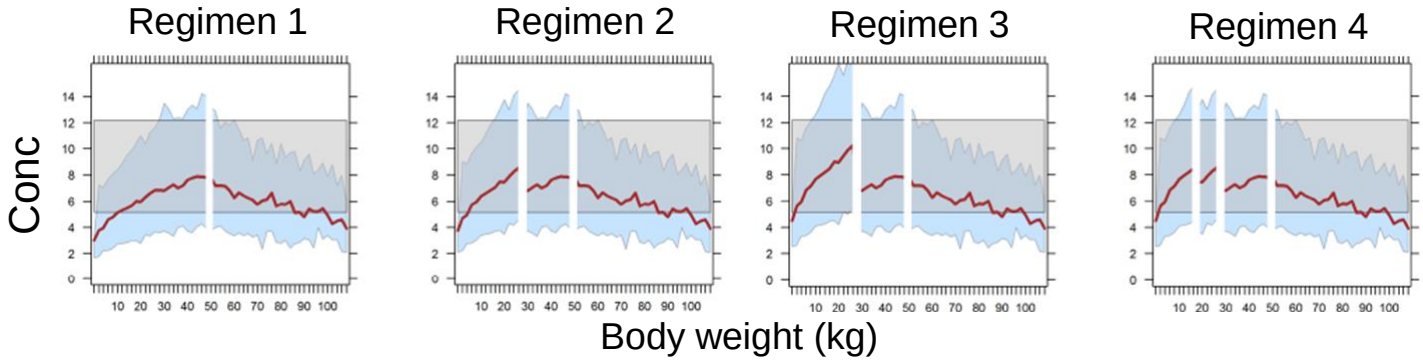
"Extrapolation of safety and efficacy to the subset of paediatric patients from 28 days to < 6 years of age on the basis of available PK and modelling & simulation data is not sufficiently supported at the moment. The lack of compelling evidence of efficacy in the paediatric phase III study population 6-18 years renders the proposed extrapolation to younger cohorts particularly difficult. For an extrapolation of safety and efficacy in this cohort, posology, titration scheme and in the broadest sense B/R have to be better understood and justified and it needs to be shown that the PK/PD relationship is similar in adults and children. Therefore, the quality of PKPD and PBPK models are crucial in this application."

There are high demands on the quality of the models used in PK bridges between adults and children, and extrapolation of efficacy and safety.

Example: New indication, paediatric

Major Objection

“The proposed dosing recommendation for adjunctive therapy in children is not supported especially not for the weight category between 20 and 30kg. The MAH is asked to reconsider the dosing scheme and present a revised proposal providing a more stable steady state concentration (Css) profile with increasing body weight (BW) and a larger overlap with the adult reference range.”



When deriving the posology in children it is important to provide a description of the body size relation and an adequate overlap between adult and paediatric exposures.

Take home messages

Or how mitigate questions from EU regulators

- Prepare the M&S reports such that assessors can review without access to data
- Provide full documentation for model development
- Provide a scientific justification/discussion for statements like “reasonably well model fit”

- The overall Benefit-Risk assessment is always done on the totality of data

References for good reporting standards (non exhaustive list)

- **Guideline on reporting the results of population pharmacokinetic analyses.** Committee for Medicinal Products for Human Use (2007)
- **Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation** EFPIA MID3 Workgroup, CPT:PSP, 2016
- **Reporting guidelines for population pharmacokinetic analyses.** Dykstra, K. et al. J. Pharmacokinet. Pharmacodyn. 2015
- **Guidelines for the quality control of population pharmacokineticpharmacodynamic analyses: an industry perspective.** Bonate, P.L. et al. AAPS J. 2012
- **Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models.** Bergstrand M et al. AAPS J. 2011