# How European Regulators Are Facilitating the Use of Modelling and Simulation:

## MSWG History, Activity and Future

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# Disclaimer

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

# From PAGE 2012

Q5: It was suggested at the EMA/EFPIA meeting that the EMA would try to increase its capabilities to assess modelling and simulation work. **What are EMA's concrete plans** and how can EFPIA help?

- EMA/EFPIA Workshop on M&S → concrete plans for EMA and CHMP
  Currently in proposal stage
- Involvement of key regulators
  Rob Hemmings (SAWP chair, CHMP member, MHRA), Tomas Salmonson (CHMP vice Chair, MPA)

M&S meeting outcome at CHMP → Structured M&S Group → Proposal: composition, scope, objectives, draft work plan* (June CHMP ORGAM)

- Current thinking (i.e. not agreed, not prioritised, not promised, but current wishes)
  A key objective: to enhance the collective competence and capacity to provide scientific advice and assessment of M&S in MAAs
  Possible areas for regulatory guidance / reflections: Update of approach to dose finding, reflection paper on M&S, guidance (Q&A) on how best to incorporate M&S in eCTD structure, reflection paper on use of M&S in support of FIM, guideline on extrapolation (with extrapolation working group), update to guideline on reporting results of population PK analyses (with PKWP)
  Training envisaged: regular programme of assessor training as guidelines are developed, follow up workshops on specific topics (e.g. dose finding)
  Collaborations envisaged: Scientific Advice Working Party, Biostatistics Working Party, Pharmacokinetics Working Party, Paediatric Committee (+ Extrapolation Working Group)

*For sample work plan, see Pharmacokinetics Working Party (http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000070.jsp&mid=WC0b01ac0580023d7c8)

PAGE 2012
Terry Shepard, MHRA, London, Slide 4

**+ other drivers:**
EMA Road map to 2015
Experience in regulatory submissions

# Objectives of MSWG

To enhance the collective competence and capacity to provide advice on and assessment of M&S in MAAs and PIPs, reducing uncertainty in B:R decisions and improving product labelling.

To advance early communication and support innovation with industry and academia in areas like FIH, dose finding, study optimisation, disease progression and extrapolation where M&S can play an important role.

To develop and communicate standards for the design, conduct, analysis and reporting of M&S 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.

# Composition

## Members

- Terry Shepard (chair, UK)
- Jacob Brogren (vice chair, SE)
- Ridha Belaiba (FR)
- María Jesús Garrido (ES)
- Frederike Lentz (DE)
- Flora Musuamba Tshinanu (BE)
- Anna Nordmark (SE)
- Gérard Pons (FR)
- Ine Skottheim Rusten (NO)
- Joe Standing (UK)
- Johannes Taminiau (NL)
- Nadine Eva Van Egmond (NL)
- Norbert Benda (DE)

} PDCO

## CHMP/SAWP

- Tomas Salmonson
- Robert Hemmings

## EMA

- Efthymios Manolis
- Spiros Vamvakas

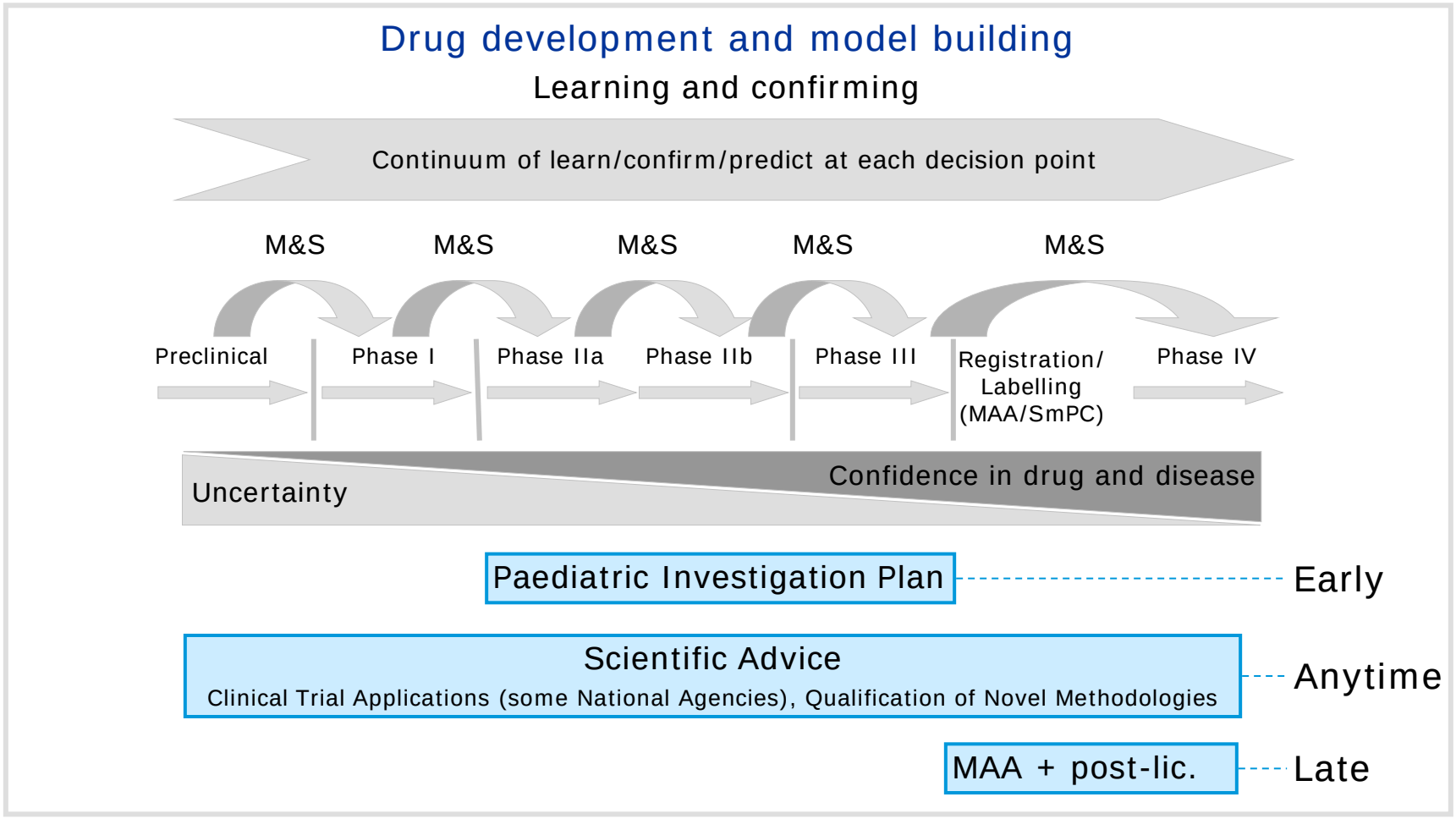
## Observers

- Petra Schmitt (PEI)

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

# M&S in European Procedures:

## When are regulatory decisions based on M&S made?




Adapted from Lalonde RL et al., Model-based drug development. Clin Pharmacol Ther 2007;82:21-32

First presented at the EMA/EFPIA Modelling and Simulation Workshop, 2011

M&S: modelling and simulation
MAA: marketing authorisation application
SmPC: summary of product characteristics

# Framework for M&S in Regulatory Review

## According to impact on regulatory decision

MHRA

### High impact

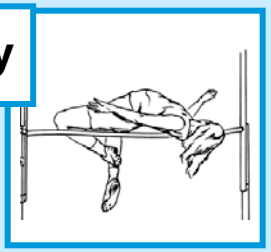
Scientific Advice, Supporting Documentation, Regulatory Scrutiny } + + +

**Replace**

### Medium impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } + +

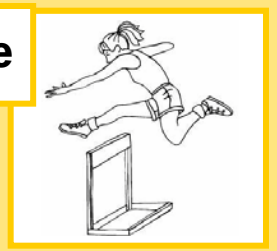
**Justify**



### Low impact

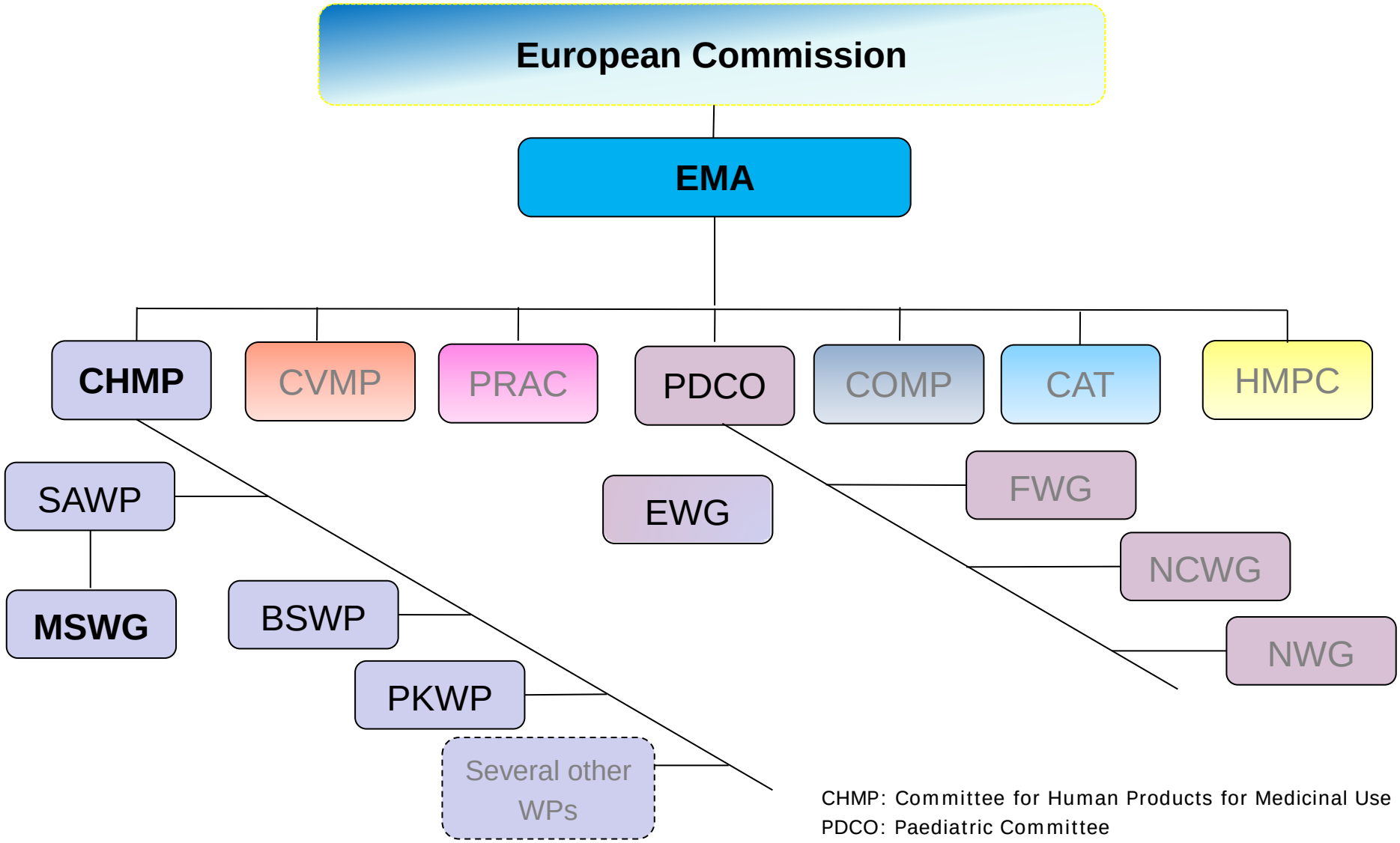
Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +

**Describe**



Impact on regulatory decision

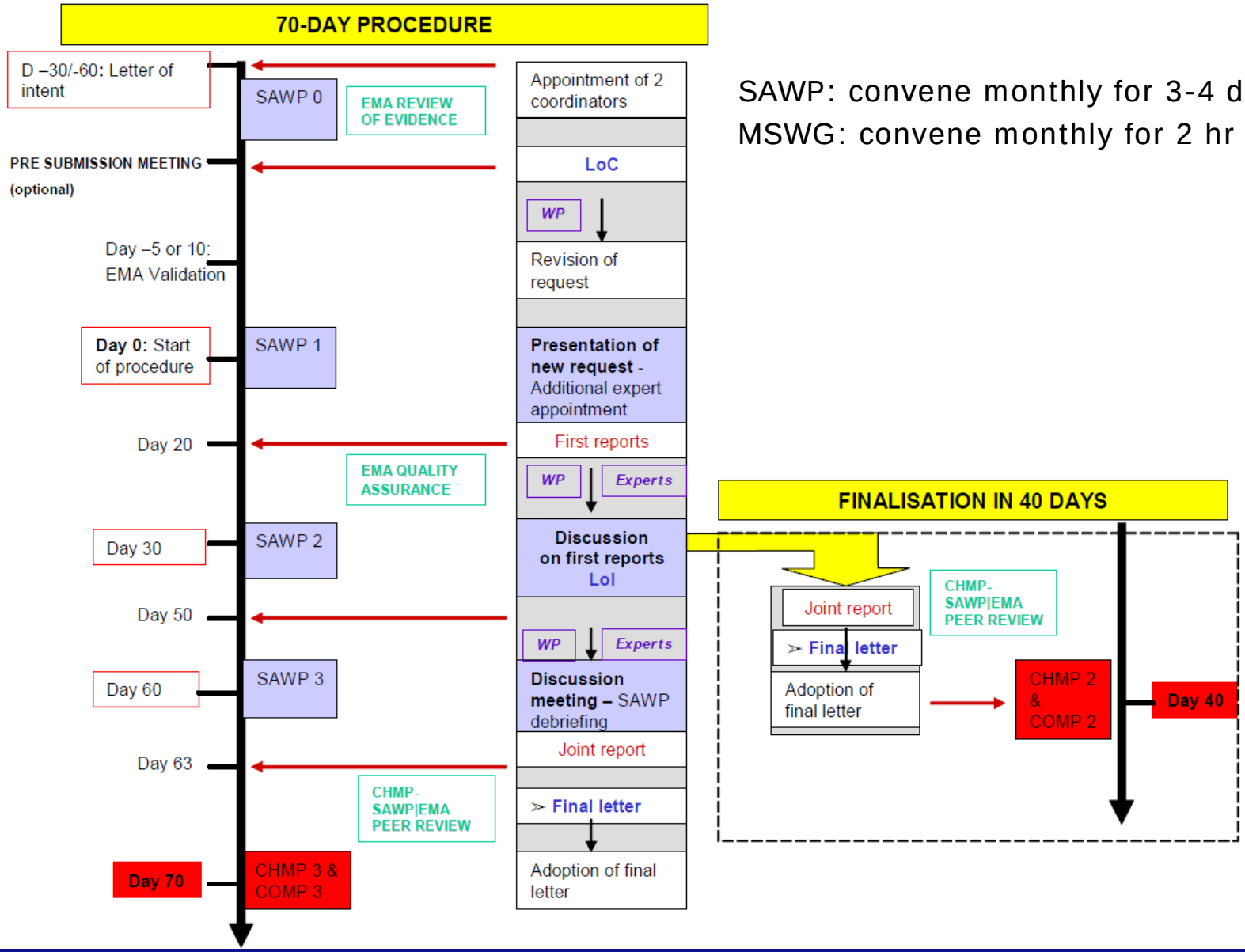
From EMA-EFPIA Modelling and Simulation Workshop, December 2011




CHMP: Committee for Human Products for Medicinal Use
PDCO: Paediatric Committee
SAWP: Scientific Advice Working Party
MSWG: Modelling and Simulation Working Group
EWG: Extrapolation Working Group
BSWP: Biostatistics Working Party
PKWP: PK Working Party

Slide adapted from Ine Rusten, NOMA

# Overview of EMA Scientific Advice Procedure




SAWP: convene monthly for 3-4 days

MSWG: convene monthly for 2 hr TC

# Typical Scientific Advice Request

- Summary
  - Background information on disease to be treated
  - Background information on the product
  - Clinical development (and quality and/or non-clinical if appropriate)
  - Regulatory status
  - Rationale for seeking advice
- Questions and Company's positions
  - Question 1

**Example**

| | |
|---|---|
| **Company question to SAWP** | Does the CHMP agree with the doses selected and the proposed dose intervals to be tested in the first phase 3 study? |
| |  |
| **SAWP question to MSWG** | Does the MSWG agree with the proposed M&S approach to support dose finding? |

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

MHRA

Date:
EMEA/209064/2007 **CONFIDENTIAL**
Procedure number:
Product Development Scientific Support Department

## MSWG report

Product name/Committee-WP

MSWG coordinator:

| |
|---|
| **1. Description of the M&S and Role in the Development**<br>*(e.g. graphical representation of model POP PK, PBPK to define dose for Ph2b studies, software, model is characterised as high impact and high standards apply)* |
| <...> |
| **2. M&S assumptions**<br>*(e.g. clearly state the model assumptions, are these assumptions supported by in house data or literature?)* |
| <...> |
| **3. Model building methodology and model evaluation. Simulation methodology and good practices**<br>*(e.g. is database adequate for model building, is NONMEM code clear, model and covariate selection, goodness of fit plots)* |
| <...> |
| **4. Issues for discussion in MSWG**<br>*(e.g. diagnostic plots show that model is not good for purpose, assumptions not supported by data, code not reflecting assumptions)* |
| <...> |
| **5. Answers to the specific M&S questions. Other comments/questions to SAWP/CHMP/PDCO**<br>*(e.g. agree with sponsor - justify position, clarification is needed in some issues-define what is missing for model evaluation and address this in a discussion meeting or in a follow up procedure, disagree -justify position)* |
| <...> |

## MSWG Template

- Internal document
- Designed for copy/paste to SAWP advice, PDCO reports

1. Description of M&S and role in development (including regulatory/company impact)
2. M&S Assumptions.
3. Model building methodology and model evaluation. Simulation methodology and good practices.
4. Issues for discussion in MSWG.
5. Answers to specific M&S questions. Other comments/questions to SAWP/CHMP/PDCO.

# Examples

| Procedure | Question to MSWG | Contribution to Final Outcome | Impact |
|---|---|---|---|
| **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:*<br>The modelling approach is generally supported.<br><br>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**.<br><br>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;<br><br>**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)*<br>*High for sponsor (limited clinical development)* |

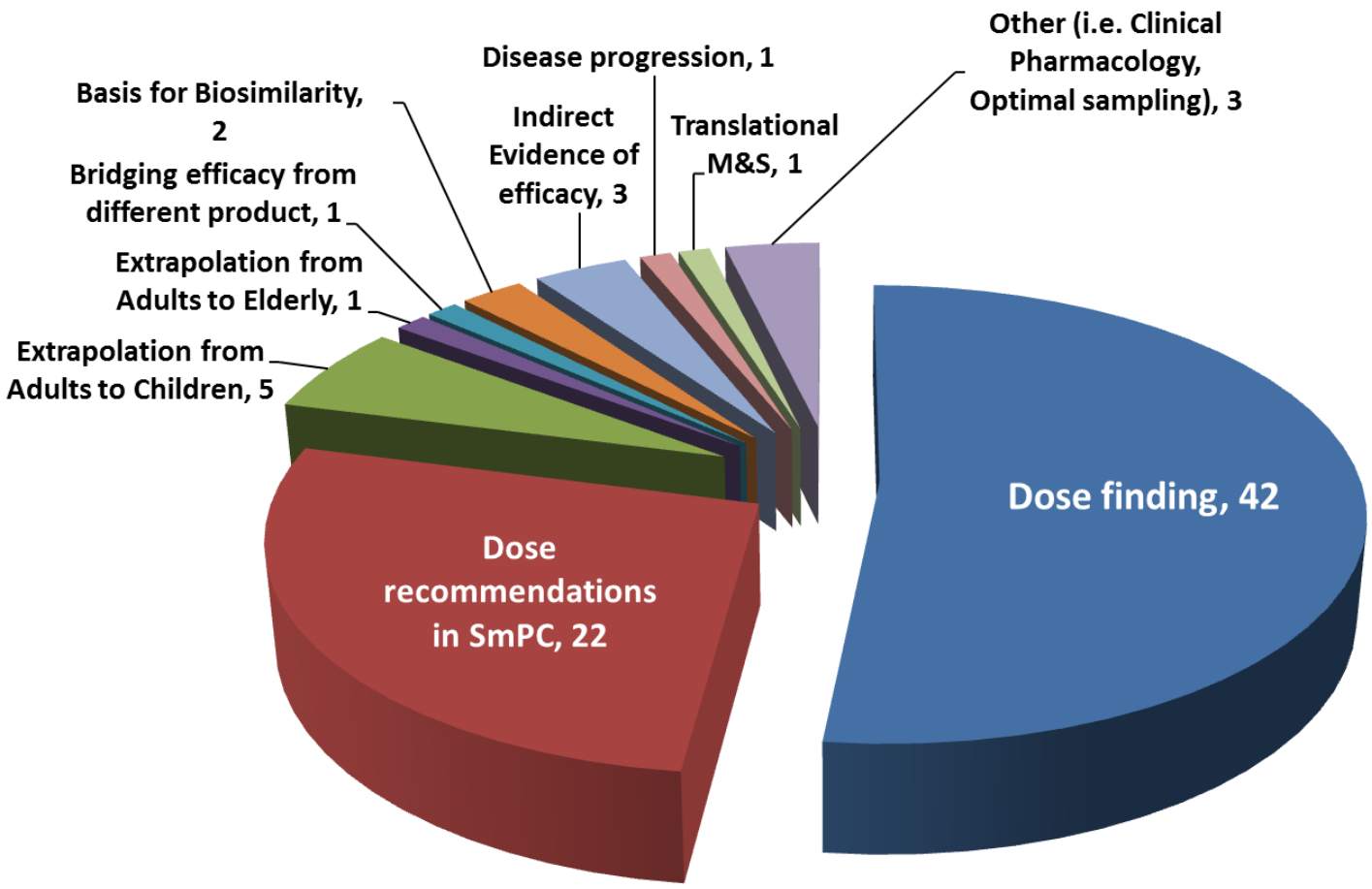
MSWG report and work plan:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000122.jsp&mid=WC0b01ac058063f485

# Examples

| Procedure | Question to MSWG | Contribution to Final Outcome | Impact |
|---|---|---|---|
| Product 3 (SAWP) | Does the MSWG agree with the proposed M&S approach to support **dose finding**? | *Text added in the final advice letter:*<br>Based on the Ph1b results the proposed dose **could be acceptable**.<br><br>However the use of modelling in the dose finding is **not considered optimal** because:<br>a) the model is based on healthy volunteer data, and<br>b) the **external validity** of the model is questionable (model did not converge with Ph1b data in patients).<br><br>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.<br><br>**This will strengthen the dose finding and will further support the Proof of Concept and the rationale for 1 pivotal trial**. | *Medium Regulatory*<br>*High for Sponsor* |

MSWG report and work plan:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000122.jsp&mid=WC0b01ac058063f485

# 59 procedures referred to MSWG in 2013




**from SAWP (51), PDCO (4), CHMP (1), and Qualification Procedures (3)**

# Progress Towards Objectives

**To enhance the collective competence and capacity to provide advice on and assessment of M&S in MAAs and PIPs, reducing uncertainty in B:R decisions and improving product labelling.**

**To advance early communication and support innovation with industry and academia in areas like FIH, dose finding, study optimisation, disease progression and extrapolation where M&S can play an important role.**

**To develop and communicate standards for the design, conduct, analysis and reporting of M&S according to the level of regulatory impact, with particular emphasis on those of high regulatory impact such as extrapolation to paediatric and elderly populations**

**2 hr TC 11 x per year**

**To increase awareness and acceptance of modelling and simulation approaches across the European national authorities.**

# Progress Towards Objectives

**To enhance the collective competence and capacity to provide advice on and assessment of M&S in MAAs and PIPs, reducing uncertainty in B:R decisions and improving product labelling.**

→ **Training**

**Facilitated by face-to-face**

**To advance early communication and support innovation with industry and academia in areas like FIH, dose finding, study optimisation, disease progression and extrapolation where M&S can play an important role.**

**To develop and communicate standards for the design, conduct, analysis and reporting of M&S according to the level of regulatory impact, with particular emphasis on those of high regulatory impact such as extrapolation to paediatric and elderly populations**

→ **Guidelines**

**To increase awareness and acceptance of modelling and simulation approaches across the European national authorities.**

# Work Plan 2014 (CHMP-endorsed)

## EMA Modelling and Simulation Working Group Plan 2014

### 1. Meetings

June, Dec

A total of 11 meetings in parallel with the scientific advice working party (SAWP) meetings, of which two will be organised as face-to-face meetings. Nine will be organised as virtual meetings.

### 2. Product-related issues

Contribution on relevant Modelling and Simulation (M&S) aspects to:

- **CHMP**: providing support to the Committee for Medicinal Products for Human Use (CHMP) on dossier evaluation, to facilitate consistency of assessments and the coherence of CHMP opinions
- **PDCO**: providing support to the Paediatric Committee (PDCO) on PIP evaluation, to facilitate consistency of assessments and the coherence of PDCO opinions
- **Scientific Advice**, Protocol Assistance and Qualification of novel methodologies at request of the Scientific Advice Working Party
- Other requests received via the CHMP from other EMA Committees and Working Parties. For example, it is envisaged that collaboration with **EMA Extrapolation Group** (for M&S application to extrapolation from adults to the paediatric population) and **GEG** (for M&S application to extrapolation from the clinical trial population to older adults) would be particularly helpful.

# Work Plan 2014 (cont'd)

## 3. CHMP guidelines and related documents

In addition to the substantive support to SAWP and PDCO and potentially growing support to CHMP, objectives for the group will be also the drafting of M&S Regulatory Guidelines/Concept Papers. Based on experience in SAWP and PDCO procedures in 2013 and the EMA/EFPIA Workshop on Modelling and Simulation held at the end of 2011, the following guidelines and related documents were identified as pivotal to facilitate appropriate regulatory application of modelling and simulation to reduce uncertainty in the benefit/risk decisions for new medicines:

- **Guideline on extrapolation** (2H2014). 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 progress

- **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.

To be released for public consultation (June/July)

# Work Plan 2014 (cont'd)

EFPIA good practice → concept paper to follow

## 3. CHMP guidelines and related documents

- **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.
- **M&S Template for assessors.** This will help streamline the regulatory approach on M&S.

In general, the priority list of guidelines/concept papers will be updated based on the experience from product related discussions. As Guidelines in specific therapeutic fields are updated, it is envisaged that the Working Group will provide useful expertise on methodological issues.

Draft concept paper PKPD in the development of antibacterial medicinal products

# Work Plan 2014 (cont'd)

EMA/EFPIA dose finding workshop, Dec 2014

EFPIA MID3

MCP-MOD

## 4. Training and Workshops

As one of the objectives of the M&S working group is to enhance the collective competence and capacity to provide scientific advice and assessment of modelling and simulation in marketing authorisation applications and PIPs, a regular programme of assessor training is envisaged. To support development where establishment of agreed regulatory standards will have the most impact, one workshop is planned together with BSWP on **dose finding, extending to both small molecules and biologics**.

As part of the longer term objective for competence development in the EU regulatory system a basic level assessors training on M&S will be organised.

## 5. Activities with external parties

It is envisaged that continued collaboration with **US FDA and MHLW/PMDA** would help the working group to achieve their objectives. Regulatory input to selected EU framework projects would help in the alignment of European regulatory needs with developing approaches in drug development. Additionally, it is envisaged that the M&S working group could make valuable contributions **to ad-hoc briefing meetings and qualification procedures on methodological topics with external parties** (pharmaceutical companies, academia, public/private partnership or patients' associations).

# Continuing our progress…

**PAGE 2012, Question 4:** What can the modelling community do in order to increase the regulatory acceptance of their work in all types of submissions?

**Regulatory acceptance is increasing through scientific advice procedure.**

### Scientific Advice

- Seek scientific advice for **medium / high impact** M&S
- Include extensive documentation, **discussion of assumptions, biological plausibility**
- Begin dialogue when not critical to approval
- **Modellers** should attend discussion meetings
- Consider **EMA or national** scientific advice

### Qualification Procedures

- Consider where appropriate (e.g. DDMore, Orbito, PBPK)
- See Efthymios Manolis presentation

### EFPIA Collaborations

- Organised feedback on guidelines
- MID3 to inform regulatory guidelines
- Dose-finding workshop with modellers, statisticians, clinicians, regulatory colleagues

# Long Term Scientific Vision

**Model informed drug development**

**Optimal and targeted drug development**

**Optimal benefit:risk**

**More informed B:R assessment and labelling**

**Better drug utilisation (target, dose)**

**Pgenetics, DDI**

**Improved health care**

# Acknowledgements

Tomas Salmonson, Chair of CHMP

Rob Hemmings, Chair of SAWP, CHMP member

Efthymios Manolis, Scientific Officer, EMA

**MSWG members, in particular**:

Jacob Brogren (Vice-Chair)

Frederike Lentz

Flora Musuamba Tshinanu

Anna Nordmark

Ine Skottheim Rusten

Joe Standing

María Jesús Garrido

Petra Schmitt

**Solange Rohu and EFPIA colleagues**