EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Role of Modelling and Simulation in Regulatory Decision Making in Europe

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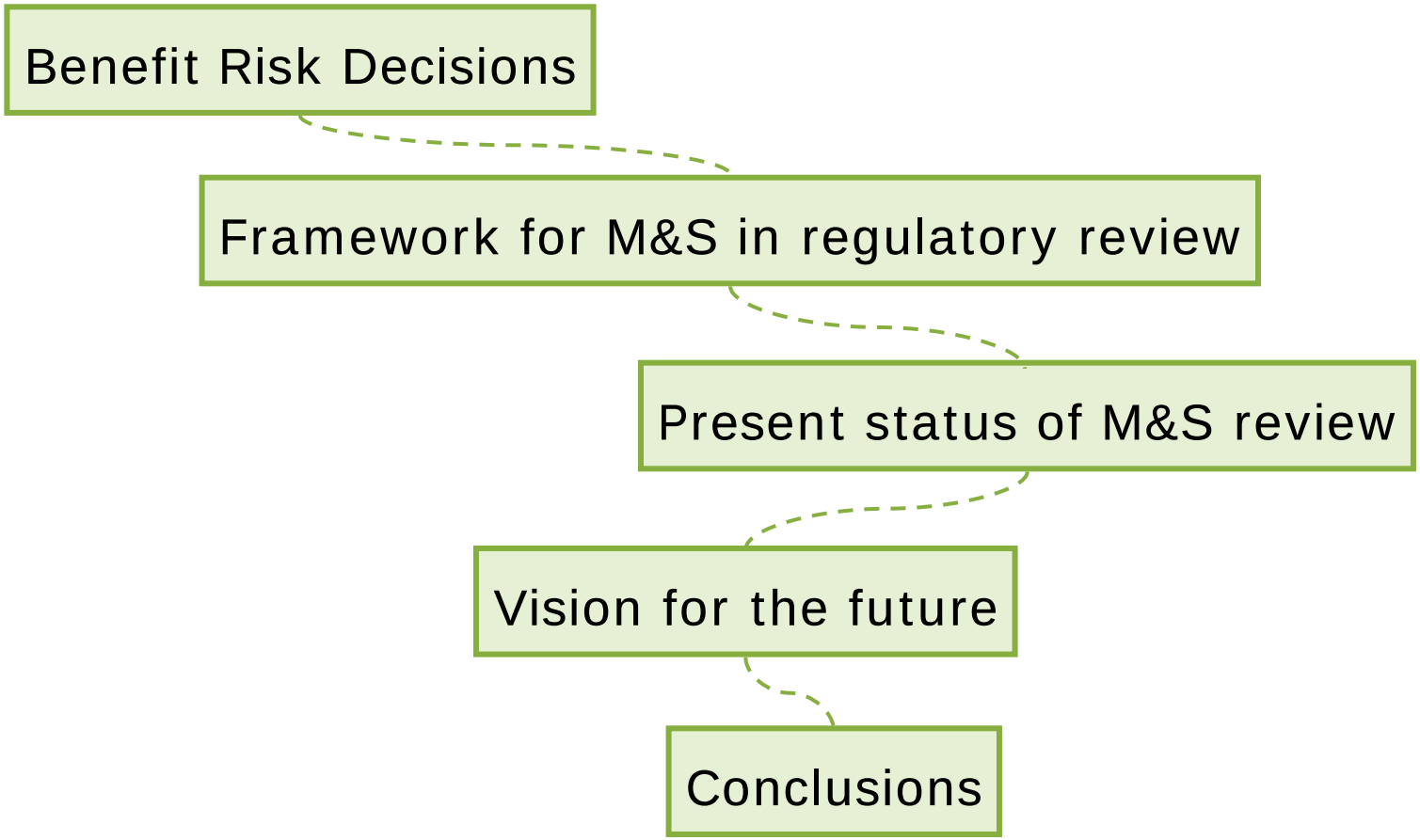
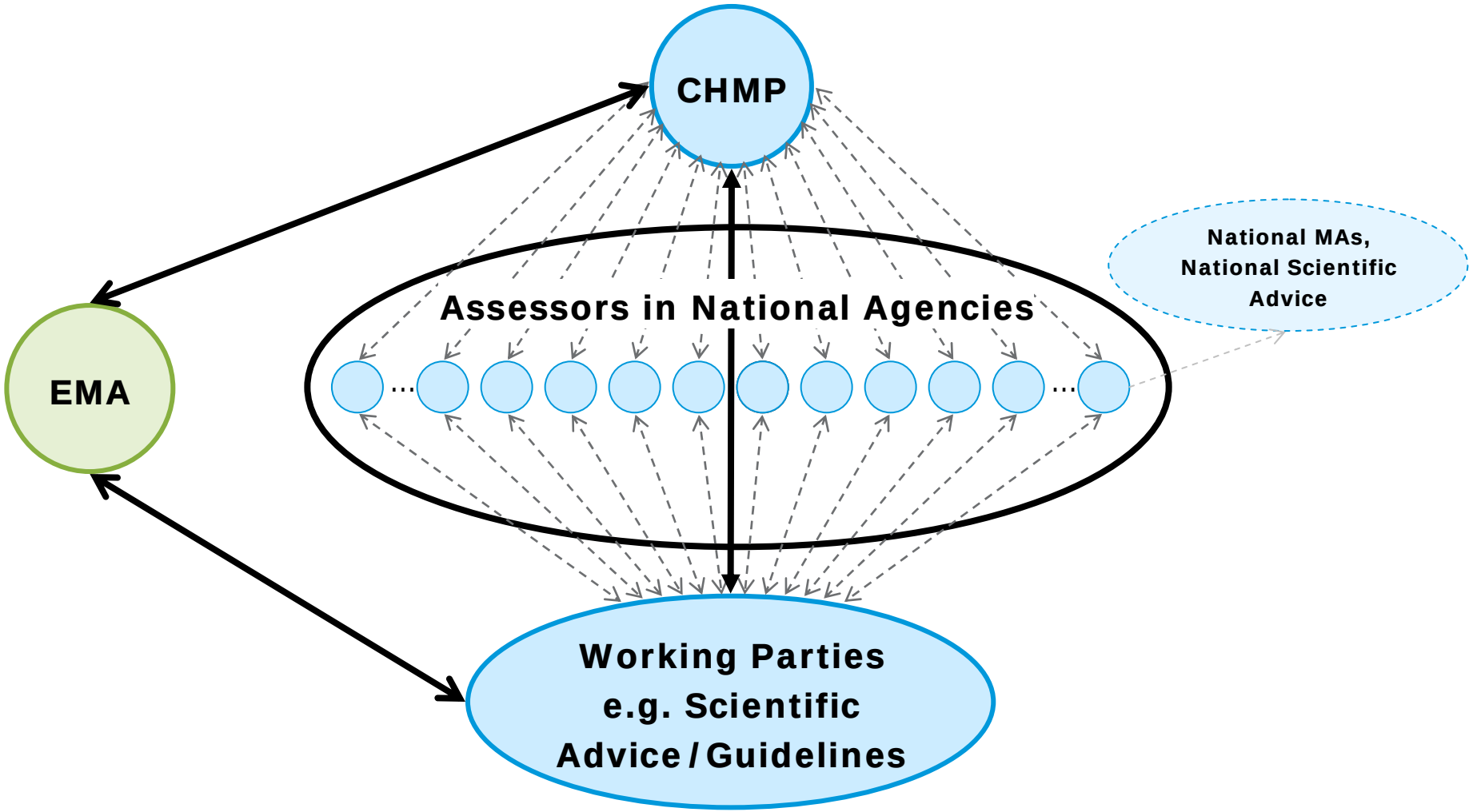
Disclaimer

The views expressed in this presentation are the harmonised views of experts across a number of European regulatory agencies and EMA, but do not necessarily reflect the official EMA position or that of its committees or working parties.

Overview


Benefit Risk Decisions
Framework for M&S in regulatory review
Present status of M&S review
Vision for the future
Conclusions

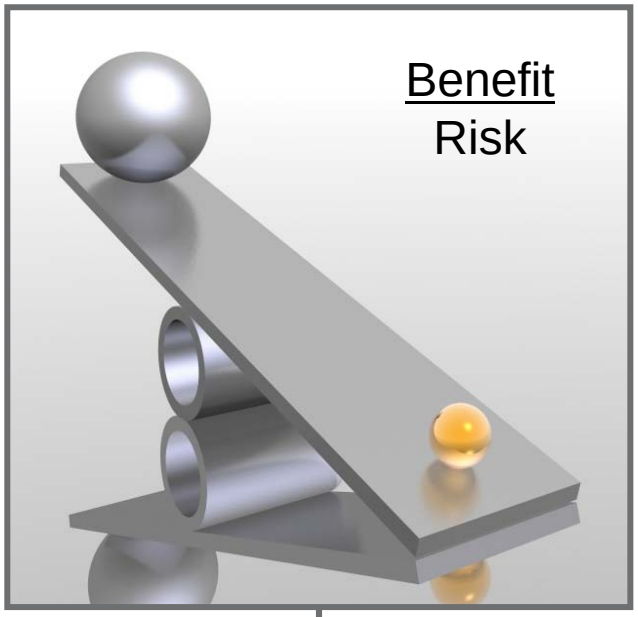
Benefit Risk Decisions



MA: marketing authorisation

Benefit Risk Decisions

Outcomes



Approval

Refusal or Withdrawal

CHMP Opinion + Annexes (SmPC, Conditions)

Indication

Specific Obligations, RMP

SmPC: summary of product characteristics
RMP: risk management plan

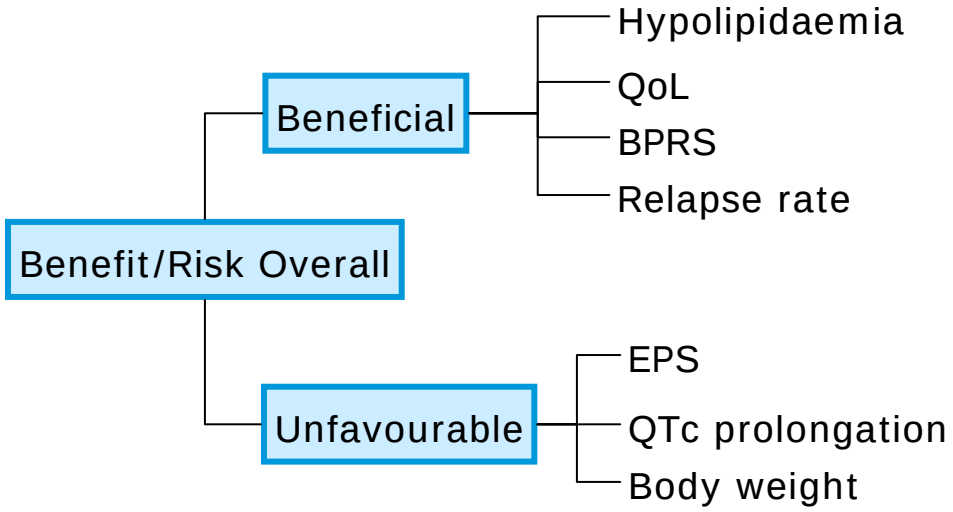
Benefit Risk Decisions

EMA Framework

Beneficial effects	Uncertainty of beneficial effects
Unfavourable effects	Uncertainty of unfavourable effects

Overall and in important subgroups, under experimental conditions reflecting clinical practice

Simplified Example:

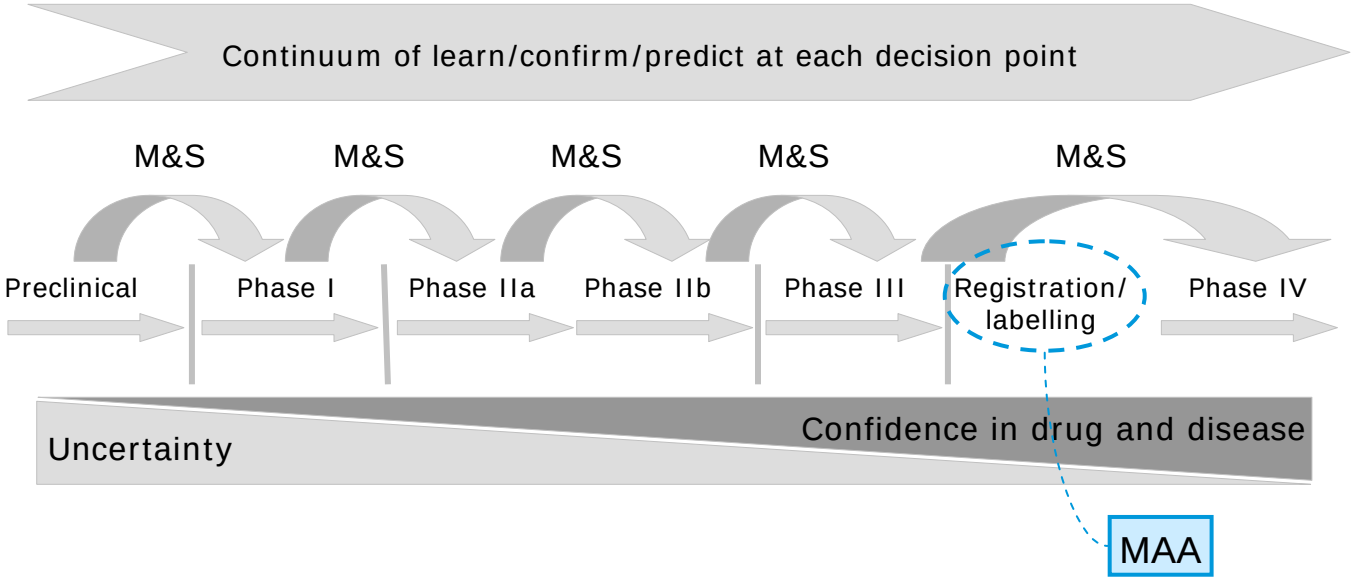


Benefit Risk Decisions

Uncertainty during drug development

Drug development and model building

Learning and confirming

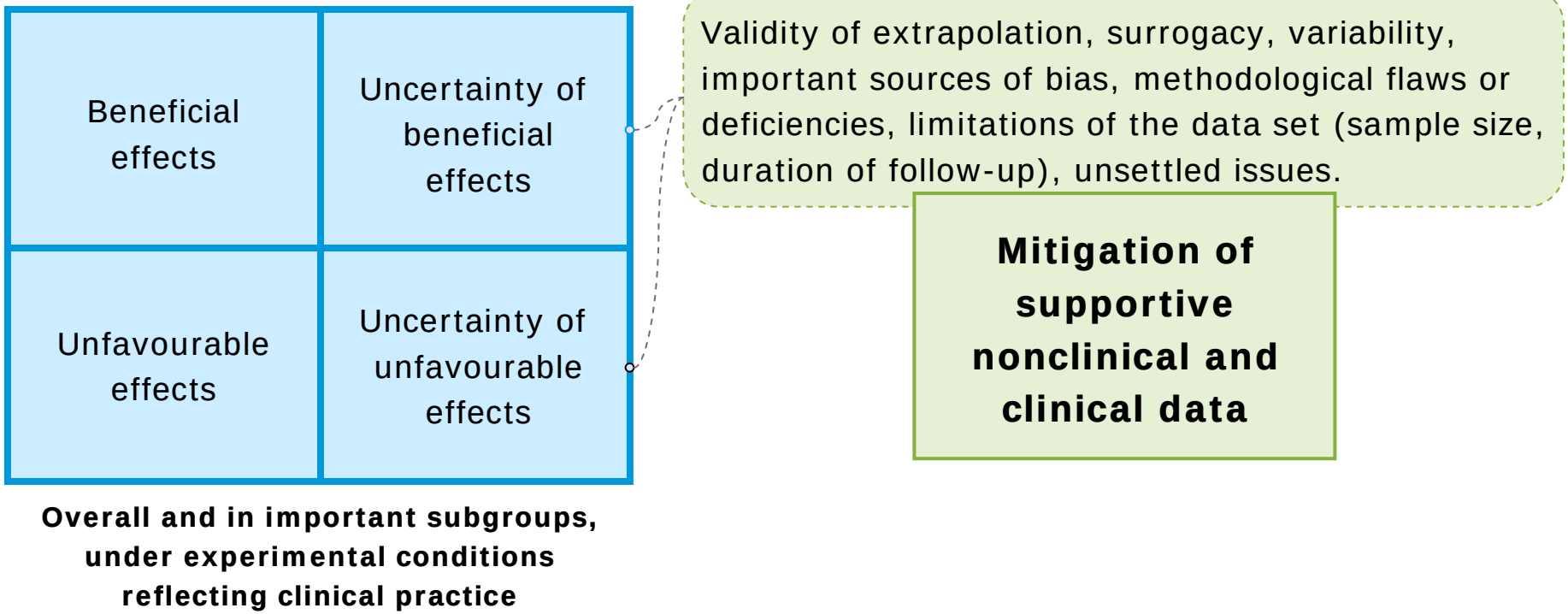


MAA: marketing authorisation application

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

Benefit Risk Decisions

EMA Framework



Framework for M&S in Regulatory Review

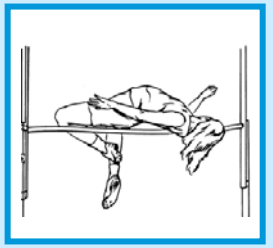
According to impact on regulatory decision

High impact

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

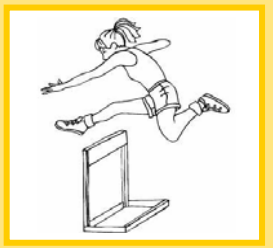
Medium impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } ++



Low impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +



Impact on regulatory decision

Framework for M&S in Regulatory Review

Low Impact

Describe

- General description of pharmacokinetic properties and exposure-response features in target population
- Interpret PK changes in important subpopulations
- Identify important covariates
- Internal decision making (hypothesis generation, learning)
- More efficient determination of dose regimen for phase III
- Verify conclusions drawn from preclinical observations and PK data in healthy volunteers
- Optimise clinical trial design for trials not pivotal to benefit-risk decision or labelling
- Descriptive content for SPC

Scientific Advice, Supporting Documentation, Regulatory Scrutiny +

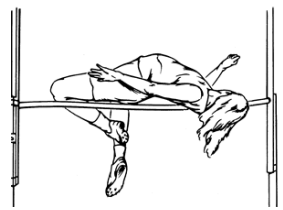
Framework for M&S in Regulatory Review

Medium Impact

Justify

- Identify PK parameters of importance for efficacy and safety leading to dose adjustment (C_{min}, AUC, C_{max}).
- Identify safe and efficacious exposure range (exposure-response in target population)
- Justify not doing a study (e.g. DDI based on PBPK and extrapolation from *in vitro* data)
- Intermediate dose levels not tested in phase II to be included in confirmatory trials
- Inferences to inform SPC content (e.g. posology when exposure is altered - elderly, impaired organ function, concomitant medications, pharmacogenetic subgroups)

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } + +



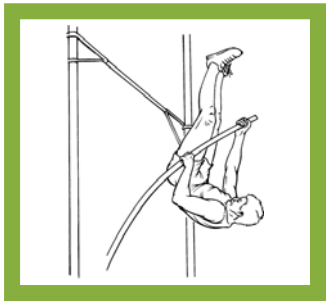
Framework for M&S in Regulatory Review

High Impact

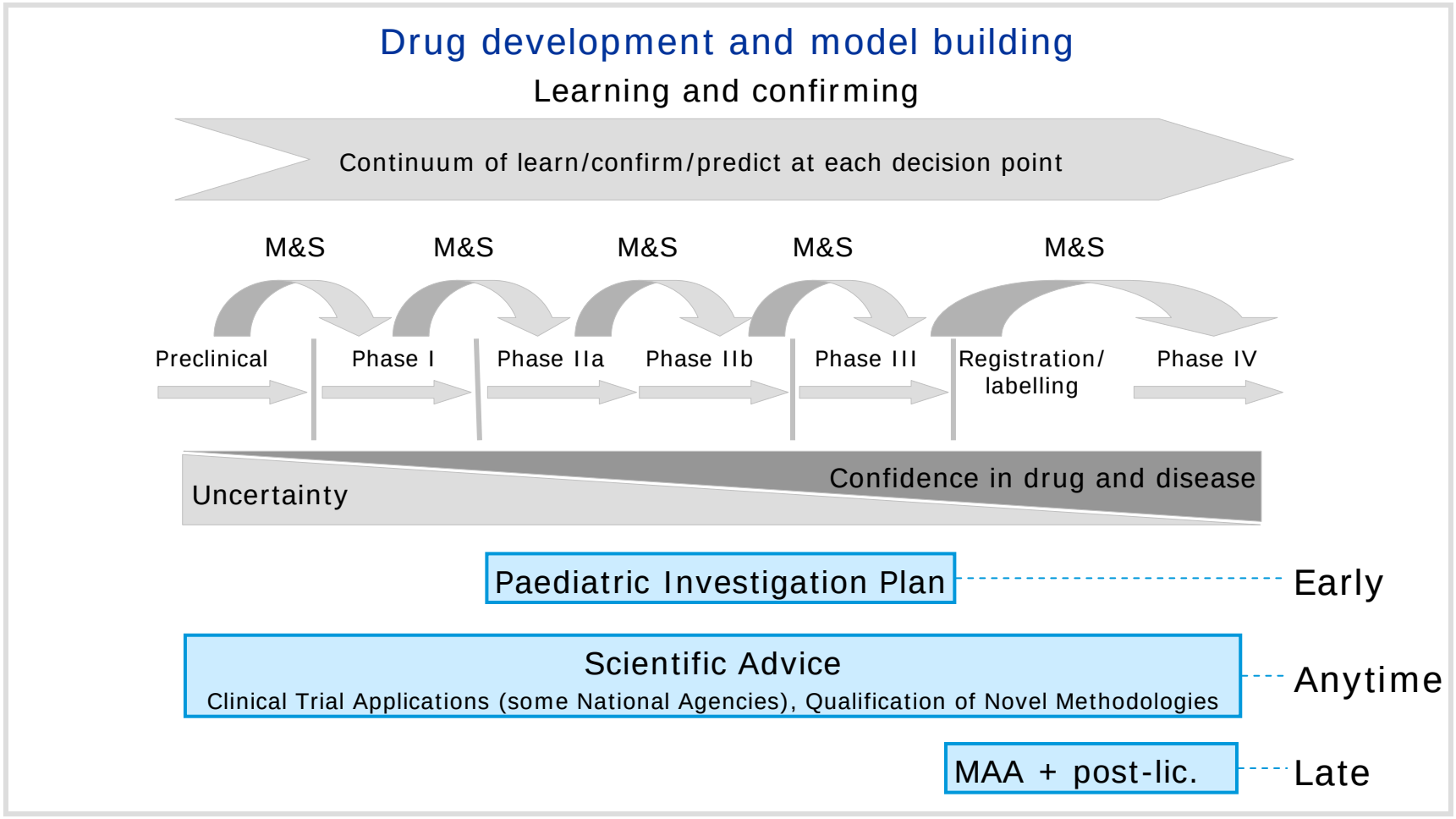
Replace

- Provide evidence of comparability (biosimilarity, biowaivers for MR formulations using IVIVC and in vitro data)
- Extrapolation of efficacy and safety from limited data (e.g. term and preterm neonates, paediatrics, small populations)
- Model-based inference as evidence of efficacy/safety in lieu of pivotal clinical data
- Key model-derived M&S components which inform SPC content in at least a subpopulation (i.e. extrapolation of efficacy and safety from limited data)

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



Present Regulatory Status of M&S Review:
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

Present Regulatory Status of M&S Review:
Type of M&S documentation reviewed

- Population pharmacokinetic (PK) models
- Population PKPD or ER models
  - biomarkers for efficacy or safety endpoint
  - clinical endpoint
- IVIVC for MR formulations
- Allometry
- IVIVC-based simulation for specification, biowaiver
- Simulations based on population PK, PKPD and/or ER models
- Simulations based on PBPK (IVIVE, DDI, paediatric, disease, interventions impacting physiology, absorption)
- Clinical trial simulation

QbD

Modelling

Simulation

ER: exposure-response; IVIVC: in vitro in vivo correlation; QbD: quality by design; PBPK: physiologically based pharmacokinetic; IVIVE: in vitro in vivo extrapolation, DDI: drug drug interaction.

Present Regulatory Status of M&S Review: **Guidelines**

Guideline on reporting the results of population pharmacokinetic analyses

Open to new methods

"Regulatory agencies … should be open to new approaches and to the concept of reasoned and well documented exploratory data analysis … ." (ICH E4: dose-response for drug registration)

Encourage M&S

Highly encourage M&S

Present Regulatory Status of M&S Review: **Guidelines**

… for example

*"…Physiological based pharmacokinetic models **may be used** as a tool…."* (Hepatic impairment guideline)

*"Establishing the relationship of drug concentrations to changes in QT/QTc interval **may provide** additional information to assist the planning and interpretation of studies …."* (QT/QTc Interval Prolongation)

Encourage M&S

*"Simulations **may** also **be used** to evaluate the in vivo relevance of inhibition observed in vitro.…Simulations **may provide** valuable information for optimising the study design…."* (Draft DDI Guidline)

Present Regulatory Status of M&S Review: **Guidelines**

*"PK/PD modelling techniques, using age appropriate and validated biomarkers, **need to be considered** to find the optimal dose. … physiologically based pharmacokinetic models to predict PK characteristics in the neonatal population may be considered if appropriate."* (Medicinal products in term and preterm neonates)

Highly encourage M&S

*"… the PK/PD relationship for an antibacterial medicinal product **should be investigated** during the drug development programme."* (PKPD in antibacterial product development)

*"Population pharmacokinetic analysis … is an appropriate methodology … in paediatric trials both from a practical and ethical point of view. …Simulations or theoretical optimal design approaches, based on prior knowledge…, **should be considered** … for the selection of sampling times and number of subjects …."* (Guideline on PK for paediatric drug development)

"…The credibility of study results may be enhanced if a dose-response relationship is seen or … where a chain of events can be identified …. Cases where no such clear chain of events exists are much less convincing and will increase the data requirements regarding robustness and persuasiveness of study results." (Clinical trials in small populations)

The Future: **Is the role of M&S in regulatory decision making evolving?**

Decrease late stage failures

Maximise information from limited patient numbers (paediatrics, orphan drugs)

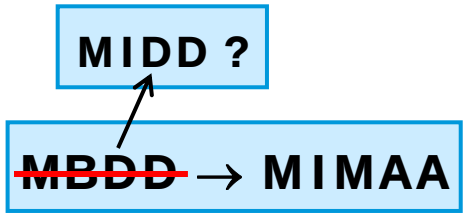
Mechanistic models for DDIs, pharmacogenetic effects, PK, PD, safety

Qualification of novel methodologies/biomarkers

Application to safety biomarkers

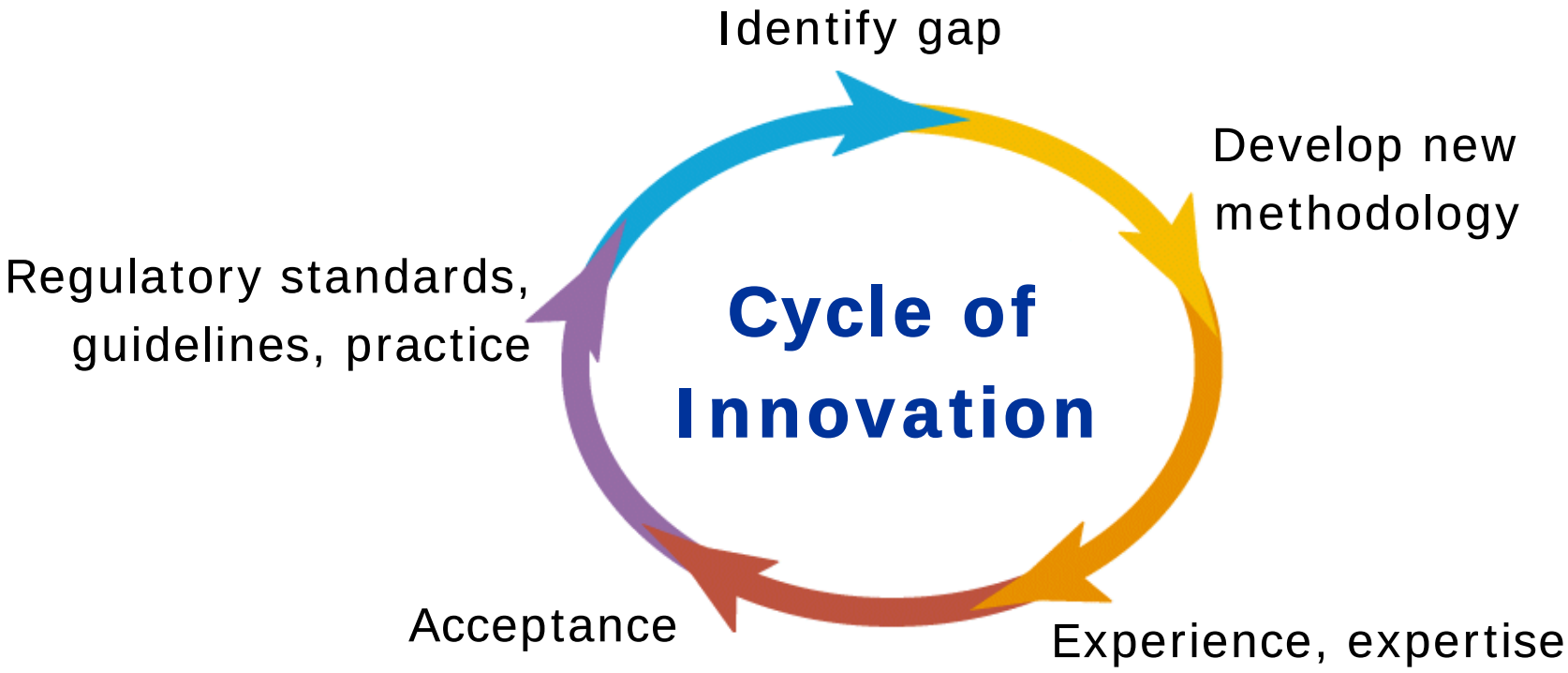
Confirmatory studies

- Disease progression models for design of phase 2 and 3 studies
- More efficient trial designs, fewer trials (single pivotal trial), shorter development programmes
- Model based analysis of primary clinical endpoints, supporting and enriching primary analysis



MBDD: model based drug development
MIMAA: model informed marketing authorisation application

The Future: **Is the role of M&S in regulatory decision making evolving?**

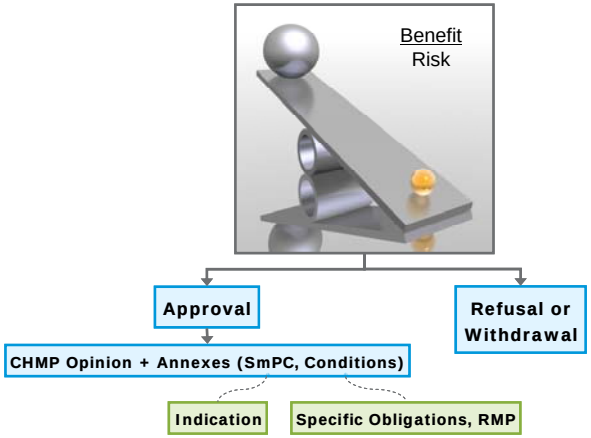


Conclusions

Endorse and support growth of M&S applications to quantify information, inform decision-making, design trials …

M&S supports best informed outcome of risk benefit decisions

- MBDD → MIMAA
- M&S in response to questions raised during assessment
- Scientific advice, documentation according to impact on risk benefit decision



Lack of M&S/quantitative pharmacology misses opportunity to mitigate uncertainty with potential impact on indication, post-approval burden, etc.

Conclusions

Dialogue will be key to extending / expanding use to agree viable objectives and assumptions and to agree documentation required.

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Publications

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Efthymios Manolis, Tariq Eldirdiry Osman, Ralf Herold, Franz Koenig, Paolo Tomasi, Spiros Vamvakas & Agnes Saint Raymond. Role of modeling and simulation in pediatric investigation plans. Pediatric Anesthesia ISSN 1155-5645 (2010).

Guidelines

Guideline on clinical investigation of medicinal products for the treatment of sepsis. (CHMP/EWP/4713/03)

Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders. (CHMP/EWP/566/98 Rev. 2 Corr.)

Guideline on clinical trials in small populations. (CHMP/EWP/83561/2005)

Guideline on reporting the results of population pharmacokinetic analyses. (CHMP/EWP/185990/06)

Guideline on the clinical development of medicinal products for the treatment of HIV infection. (EMEA/CPMP/EWP/633/02 Rev. 2)

Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease. (CHMP/EWP/1343/01 Rev. 1)

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Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins. (CHMP/EWP/89249/2004)

Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. (CPMP/EWP/2339/02)

Guideline on the investigation of medicinal products in the term and preterm neonate. (EMEA/536810/2008)

Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. (EMEA/CHMP/EWP/147013/2004)

References (Publications and Guidelines)

Guidelines (continued)

ICH Topic E 11. Note for guidance on clinical investigation of medicinal products in the paediatric population. (CPMP/ICH/2711/99)

ICH Topic E 14. The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for NonAntiarrhythmic Drugs. (EMEA/CHMP/ICH/310133/2008)

ICH Topic E 4. Note for guidance on dose response information to support drug registration. (CPMP/ICH/378/95)

ICH Topic E 7. Note for guidance on studies in support of special populations: geriatrics. (EMA/CHMP/604661/2009)

Note For Guidance On Modified Release Oral And Transdermal Dosage Forms: Section II (Pharmacokinetic And Clinical Evaluation) (CPMP/EWP/280/96/ Corr*)

Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function. (CHMP/EWP/225/02)

Note for guidance on the investigation of drug interactions. (draft) (EMA/CHMP/EWP/125211/2010)

Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products. (CPMP/EWP/2655/99)

Points to consider on application with 1.meta-analyses, 2.one pivotal study (CPMP/EWP/2330/99)

Reflection paper on the use of pharmacogenetics in the pharmacokinetic evaluation of medicinal products. (EMEA/128517/2006)