EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CHMP Qualification of Novel Methodologies

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An agency of the European Union

Outline

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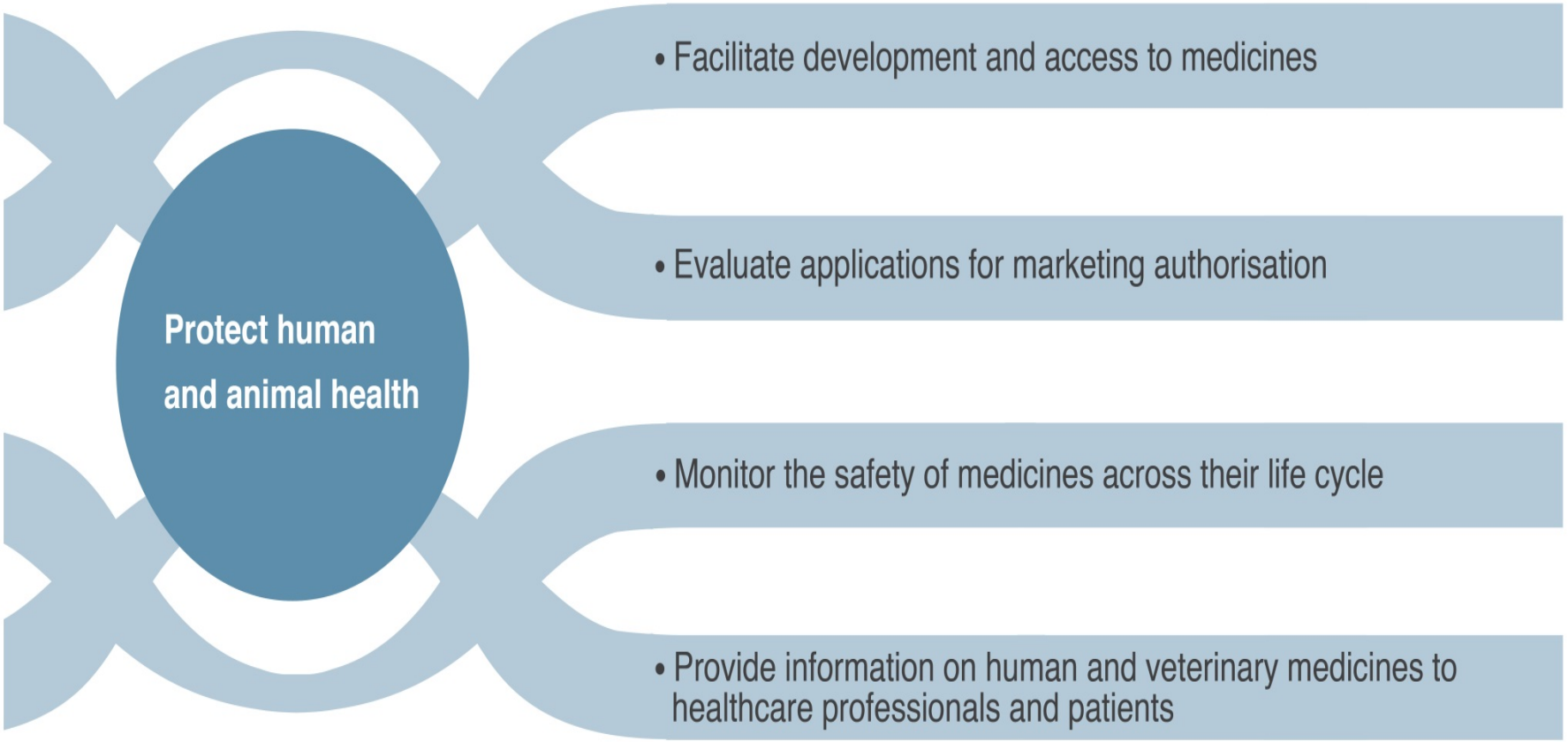
The role of regulators as **Enablers** for Drug Development

Qualification of Novel Methodologies

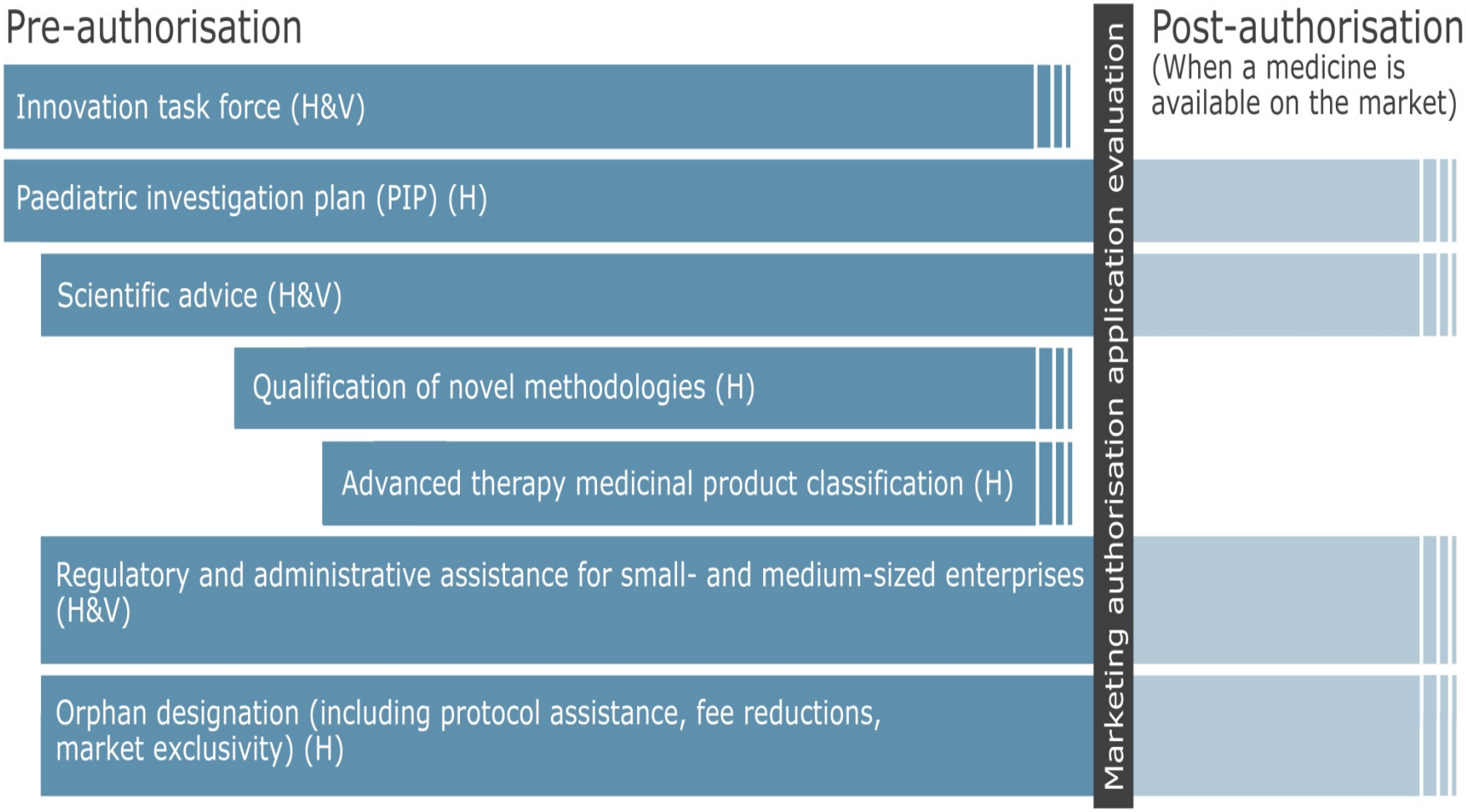
MCP-Mod

Application to PBPK

What do we do?


Protect human and animal health
• Facilitate development and access to medicines
• Evaluate applications for marketing authorisation
• Monitor the safety of medicines across their life cycle
• Provide information on human and veterinary medicines to healthcare professionals and patients

Supporting research and innovation of medicines



Qualification

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CHMP Qualification Advice (Confidential) on future protocols and methods for further method development towards qualification

CHMP Qualification Opinion (Publicly Available) on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data

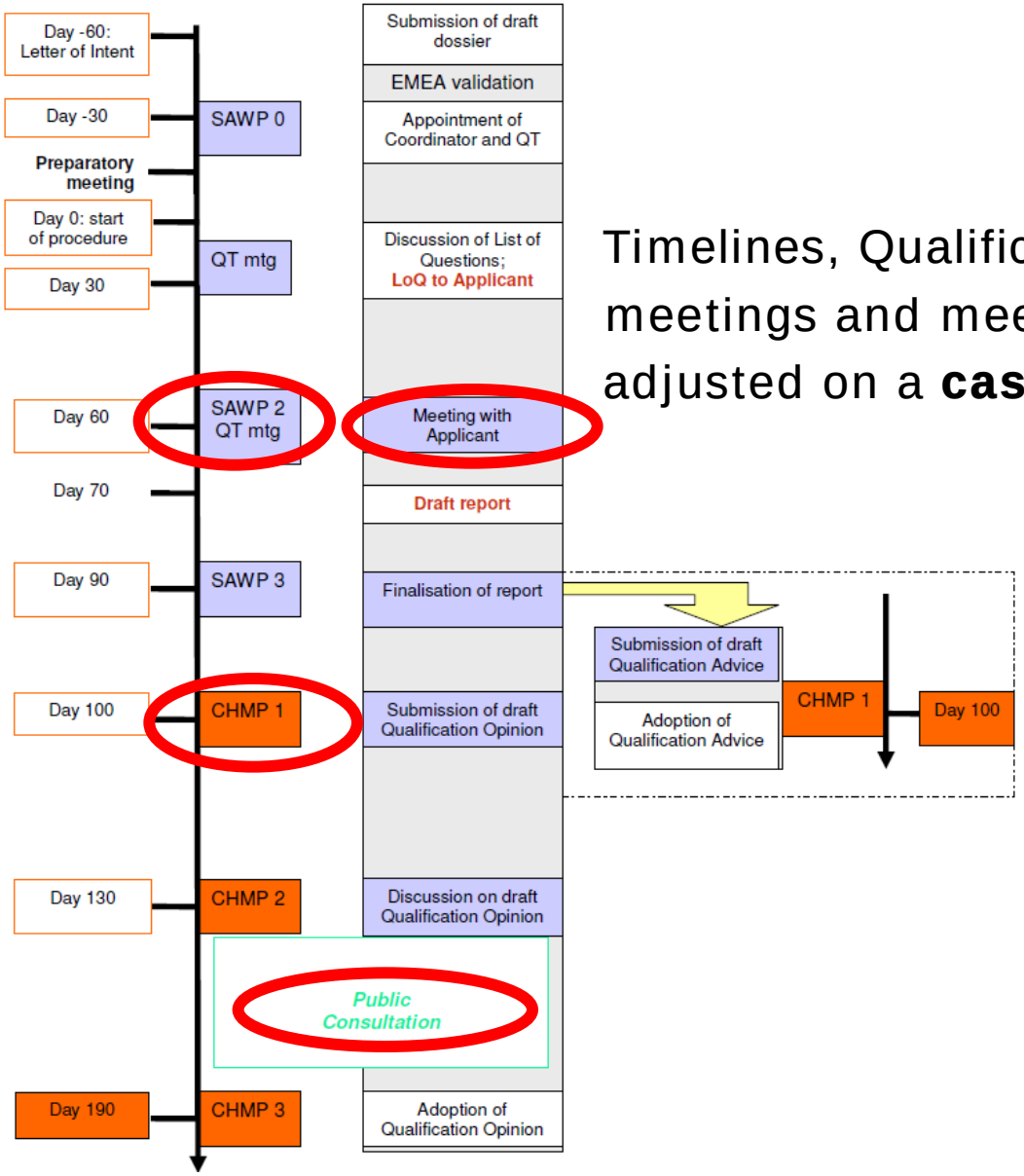
Fees & Exemptions applicable

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/06/WC500208145.pdf

Who can apply? Consortia, Networks, Public/Private partnerships, Learned societies, Pharma, CROs, Software developers,...

Vision: Speed up/optimise drug development and utilisation, improve public health

Qualification Procedure



Timelines, Qualification Team (QT) meetings and meetings with applicant adjusted on a **case by case basis**

Guidance and Final Qualification Opinions available on the EMA website

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0

Qualification Scope and Methods

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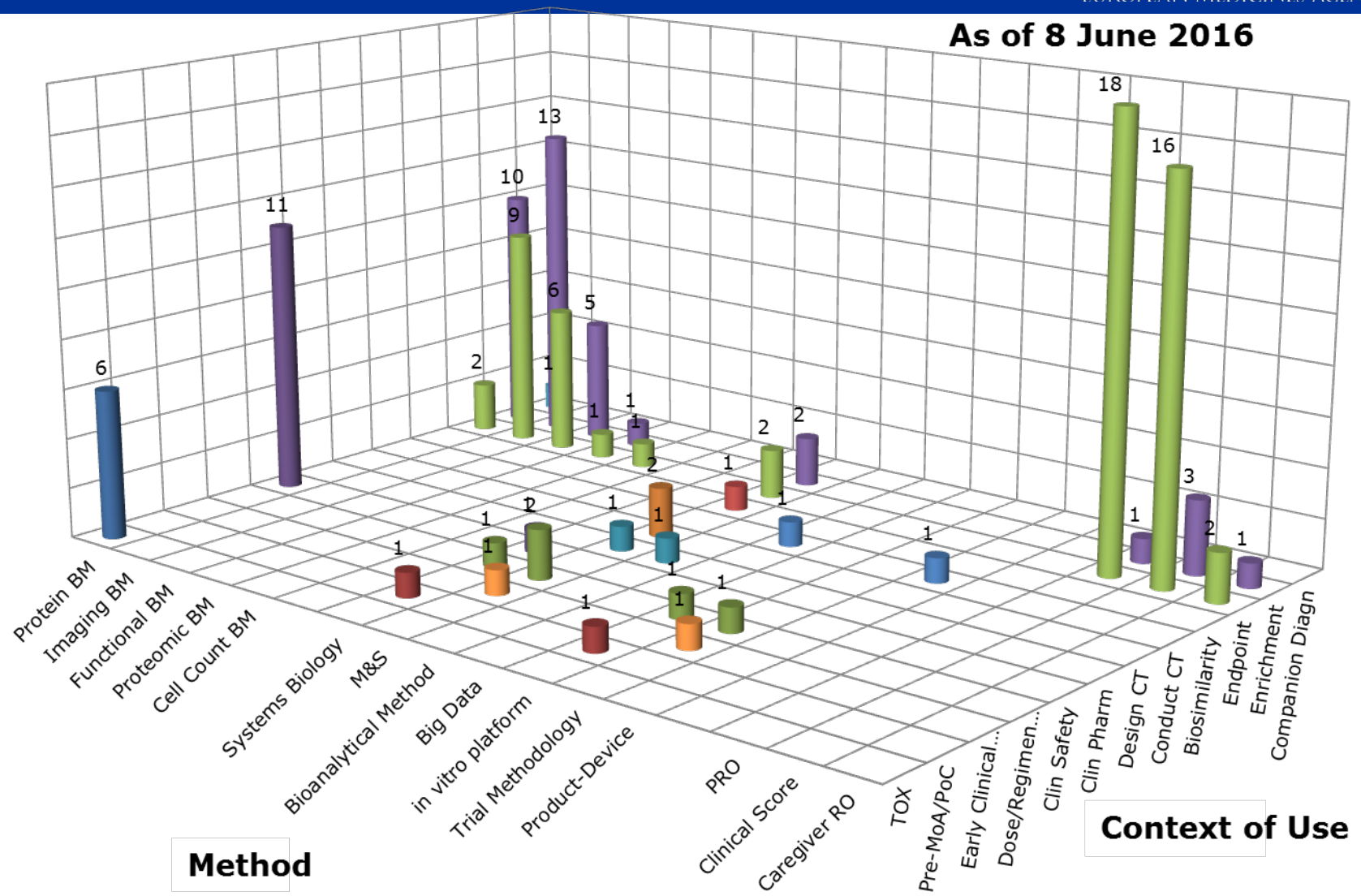

MCP-Mod Qualification Request

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Novartis seeks qualification of MCP-Mod as an

Efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty

MCP-Mod stands for: Multiple Comparisons & Modelling

The data supportive of this request consists of the following elements:

- **Worked examples**, extensive **simulations and real-life case studies** to describe and quantify the performance
- References from **medical and statistical literature** to illustrate applicability

A multidisciplinary **qualification team** was formed:

Robert Hemmings (coordinator)

David Brown, Kolbeinn Gudmundsson, Ferran Torres, Jacob Brogren, Kersti Oselin, Jacques Ropers, Sofia Friberg-Hietala, Efthymios Manolis

MCP-Mod Methodology

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Trial Design Stage

General design considerations

Determination of suitable study population, endpoints, etc.

Set of candidate models

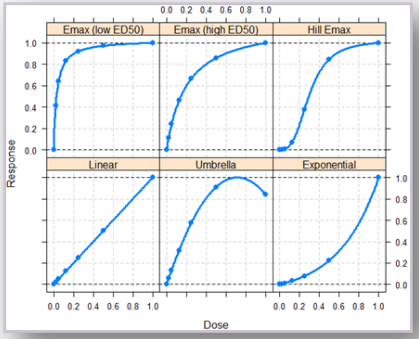
Pre-specification of candidate dose-response models based on available information (similar compounds, mode of action)

Optimal statistical tests

Optimized for candidate dose-response shapes

Design evaluations

Dose determination and sample size calculation to achieve targeted performance characteristics



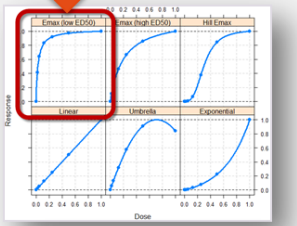
Trial conduct

$p < \alpha$?

Trial Analysis Stage

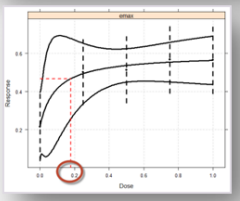
MCP step

- Assessment of dose-response signal using contrast tests
- Model selection (or model averaging) out of the set of significant models



Mod step

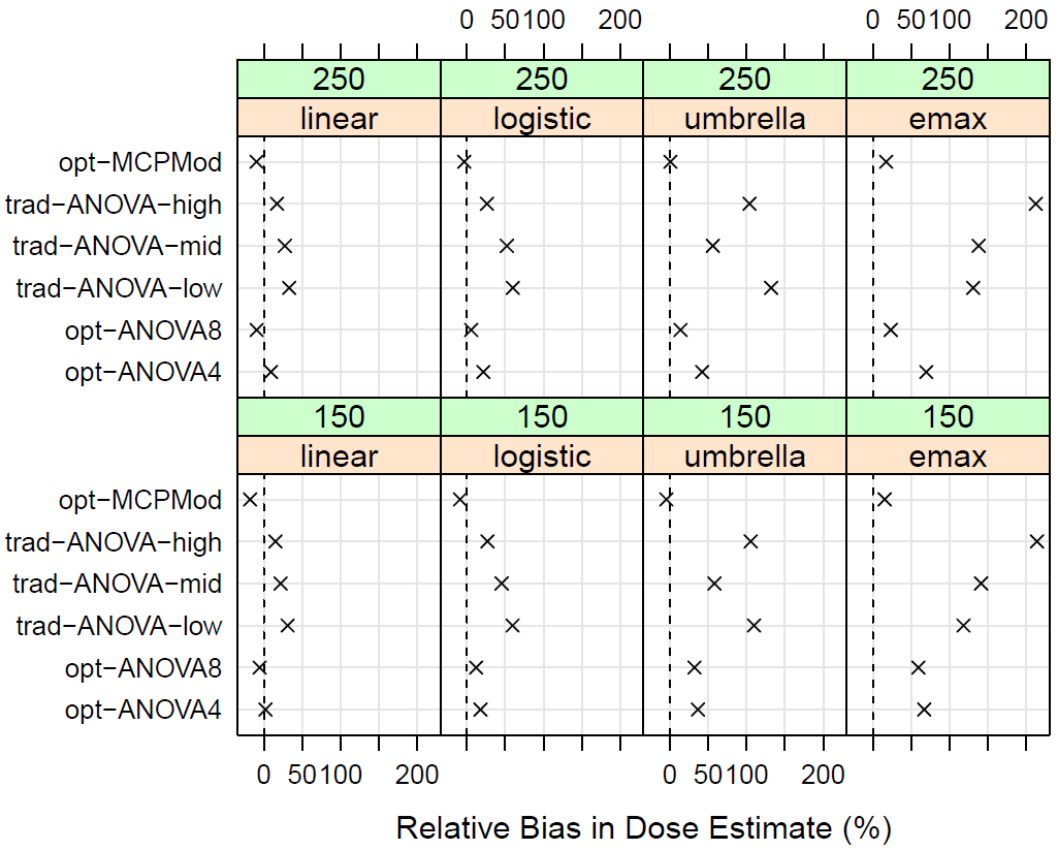
Dose-response and target dose estimation based on selected model(s)



Difference to traditional pairwise comparisons

- Use of dose-response modelling
- But, taking model uncertainty into account at *design* and *analysis* stage

MCP-Mod Example of Sim outputs



Run 10000 clinical trial simulations for each scenario

One of the outputs of interest: **Target Dose**

One of the Performance Metrics:

$$pBias = 100E(\hat{d}_{targ} - d_{targ})/d_{targ}$$

MCP-Mod provides roughly unbiased estimates of the **target dose** in almost all scenarios

The ANOVA type approaches are all slightly upwards biased

MCP-Mod Final Qualification Opinion

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23 January 2014
EMA/CHMP/SAWP/757052/2013
Committee for Medicinal Products for Human Use (CHMP)

Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty

Draft agreed by Scientific Advice Working Party	5 September 2013
Adopted by CHMP for release for consultation	19 September 2013[1]
Start of public consultation	15 October 2013[2]
End of consultation (deadline for comments)	24 November 2013[3]
Adoption by CHMP	23 January 2014

MCP-Mod Final Qualification Opinion

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CHMP **qualified** MCP-Mod as an **efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty**

The performance of MCP-Mod against other model-based approaches has **not** been appraised

MCP-Mod represents **one tool in the toolbox**

Post Qualification opinion

EMA/EFPIA dose finding workshop, 04 - 05 Dec 2015

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/04/WC500185864.pdf

MCP-Mod acceptance in regulatory submissions, e.g. scientific advice

Increased regulators focus on dose-exposure-response characterisation

Application to PBPK

The **MCP-Mod Qualification** was presented to exemplify the concept, the definitions, timelines, resources & documentation needed

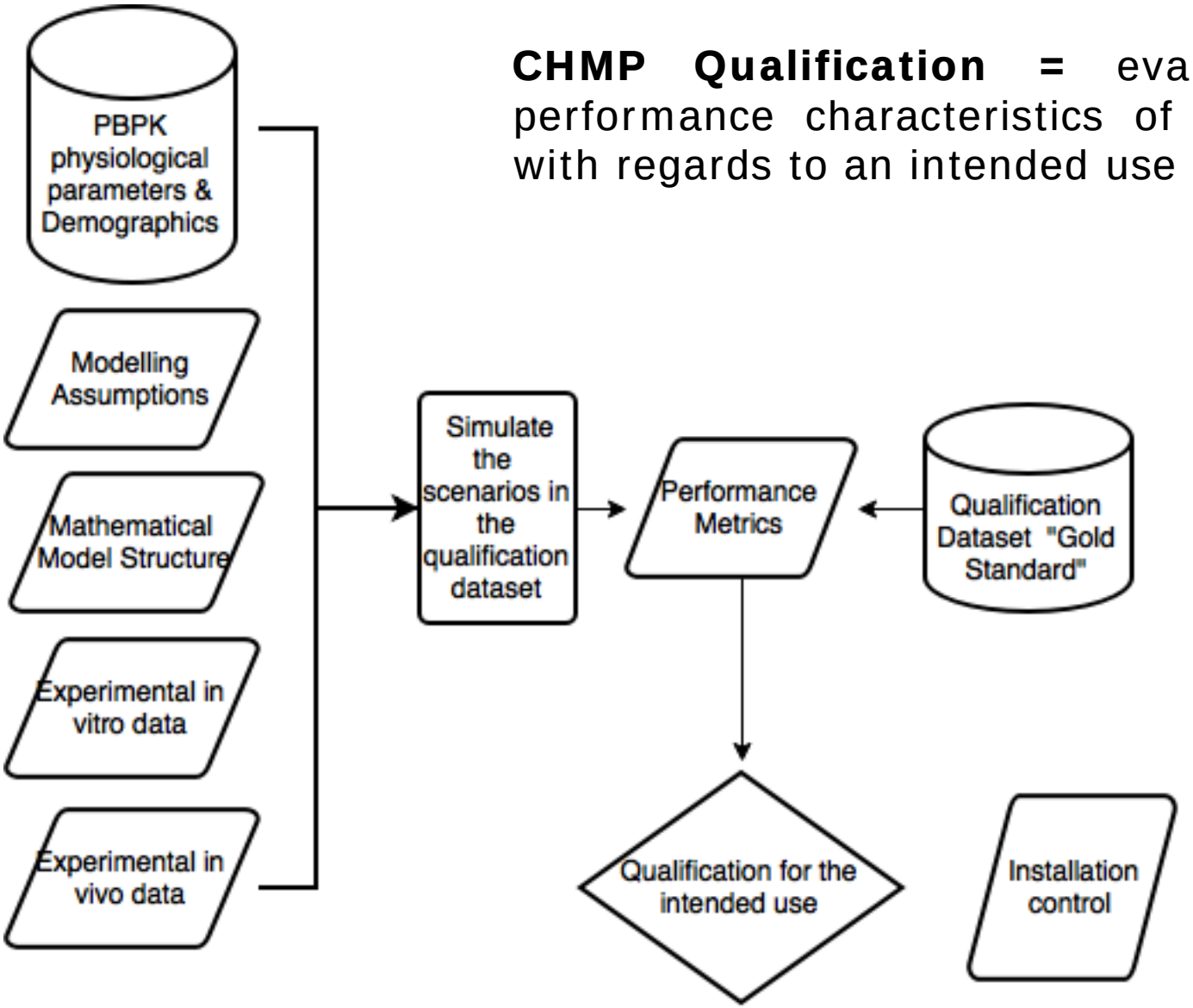
The Qualification of a PBPK platform is different

Lots of physiological parameters

Lots of assumptions, which are often not statistically evaluable, but we have to accept at *face value* based on what we know about physiology, pharmacology, *in-vitro* data and compounds with similar ADME characteristics

Application to PBPK

CHMP Qualification = evaluation of performance characteristics of a method with regards to an intended use



Application to PBPK

Critical points for Qualification of PBPK platform

- Simulation outputs and performance metrics for an intended use
- Acceptance criteria for these metrics
- Datasets used as a “Gold Standard”
- Clarity on model assumptions and ideally consensus on physiological and demographic parameters

- Generalizability of the findings to new drugs
- Standardization of experimental settings for defining in vitro parameters
- Acceptance criteria for the investigational drug PBPK model informed by the platform qualification exercise and by the intended use


Thank you
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Any questions ?