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Physiologically Based Biopharmaceutics Modeling (PBBM) Best Practices For Drug Product Quality: Regulatory and Industry Perspectives

Application of PBBM in regulatory submissions – EMA

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EMA Guideline: Reporting of PBPK Modelling and Simulation

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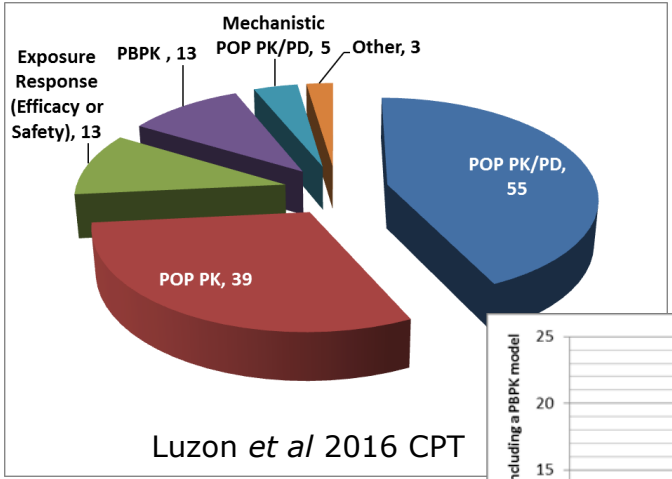
13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

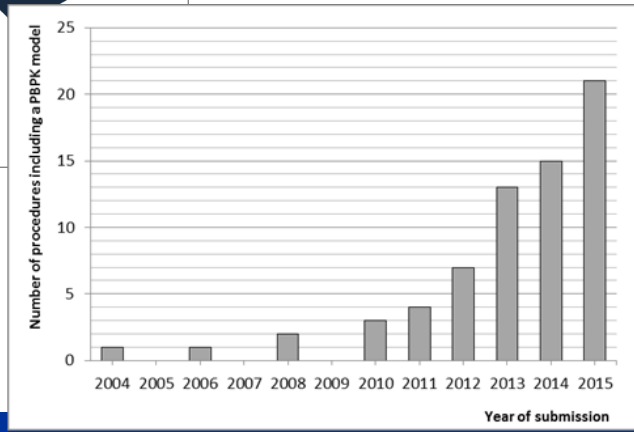
Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetics Working Party	May 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	29 July 2016
End of consultation (deadline for comments)	31 January 2017
Agreed by Modelling and Simulation Working Group	October 2018
Agreed by Pharmacokinetics Working Party	October 2018
Adopted by CHMP	13 December 2018
Date of coming into effect	1 July 2019

PBPK submissions to EMA



Luzon *et al* 2016 CPT



What do we generally ask for?

- Platform qualification of the intended use (in case of medium or high regulatory impact applications)
  - Numerical and computational verification of the platform;
  - Clarity on the assumptions and their impact;
  - Prediction performance of the model: To confirm model is valid by comparing with *in vivo* studies (e.g. pharmacokinetic studies with different doses, repeated dosing, formulations etc.)
  - Sensitivity analysis for key parameters.

Framework for M&S in Regulatory Review

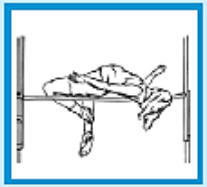
According to the impact on regulatory decision

High impact ← M&S to replace

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

Medium impact ← M&S to justify

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } ++



Low impact ← M&S to describe

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +

Impact on regulatory decision

level of documentation

http://www.emea.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118262.pdf

Common deficiencies

- **Context of use** of the model **unclear**;
- **Input parameters** (e.g. the source of Log P, pKa permeability) and their **uncertainty** should be **sufficiently** discussed;
- **Model verification** should be well described/performed;
- **Model prediction performance** should be sufficiently supported by relevant (human) data**.**
- The **clinical relevance** of any **mis-prediction** should always be **discussed;**
- **Dissolution method** not **properly developed/discussed;**
- **Formulations** used for the model development/validation **not** well **described/justified**, or **irrelevant.**

eCTD – where to present

- ✓ **Multidisciplinary issue**
- ✓ **Module 3 – ok**
- ✓ **Module 5 – ok**

meaningful summaries in **module 2**, particularly for *high impact* M&S, e.g., replacement of clinical trials or justification of otherwise unacceptable specifications

- ✓ **Depends on driver (intended purpose)**
- ✓ **Crossreference recommended to avoid repetition & facilitate review**

PBBM reports: be detailed, elaborate.

Do not assume, assumptions, starting point, intention is known to reviewer

Consolidated 3-year work plan for the Methodology Working Party (MWP)

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15 December 2022
EMA/CHMP/58124/2023
Human Medicines Division

Consolidated 3-year work plan for the Methodology Working Party (MWP)

Chairperson: Kit Roes

Vice chair: Kristin Karlsson

Work plan period: May 2022 – December 2024 (with a first review point after one year)

https://www.ema.europa.eu/en/documents/work-programme/consolidated-3-year-work-plan-methodology-working-party-mwp_en.pdf

Methodology Working Party (MWP) Consolidated 3-year work plan

- Q&A on reporting and qualification of PBPK models;
- Q&A on food effect assessment and drug interactions in the gastrointestinal tract;
- Concept Paper on Model Informed Bioequivalence;
- Identify applications where M&S is/should be proposed as key aspect of the regulatory submissions, develop or adapt the standards and implement a framework for optimal and highest quality regulatory input.
- **Workshops** identified to be initiated in 2022-23: Physiologically based biopharmaceutical modelling (PBBM) with industry and international regulators.

Take home message

- PBBM is a useful tool building strong scientific rationale;
- Widely used to inform drug development decisions;
- However subject to assumptions and uncertainties, especially when used for predictions;
- Can be used to improve/inform regulatory decision making;
- Model scrutiny depends on impact of model on the regulatory decision and product labelling;
- Discussion of PBBM results require review at a technical level and multidisciplinary dialogue (e.g. MWP, QWP);
- Early dialogue with regulators recommended.

Acknowledgements

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Any questions?

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