EMA draft Guideline on the qualification and reporting of Physiologically Based Pharmacokinetic (PBPK) Modelling and Simulation

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The opinions expressed during this presentation are those of the speaker, and not necessarily those of the MPA or the European Medicines Agency.
Outline

• Europe and EMA
• Why a PBPK Guideline in Europe?
• Qualification of the PBPK platform for the intended use
EU member states working together under the EMA umbrella
Modified release dosage forms: IVIVC and PBPK

- Level A models

Two general categories of mathematical approaches to IVIVC modelling are one- & two-stage methods. One stage approaches include convolution-based and differential equation-based methods and use of PBPK models.

Where PBPK models are utilised for IVIVC development, it will be necessary to demonstrate that the model predicts the RFD data as well as the MR formulation data. Sufficient data needs to be submitted to support the performance of the model.
Why a PBPK Guideline in Europe?

Guideline on the qualification and reporting of Physiologically Based Pharmacokinetic (PBPK) Modelling and Simulation

Draft was released in July 2016
Public consultation was due 31 Jan 2017

NB! In Europe draft Guidelines are not in to force.
Increase in PBPK submission to EMA

Luzon et al 2016 CPT
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<td><strong>Drug parameters</strong></td>
<td>Comparison between strengths/formulations</td>
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up to 31st December 2015*

*Note: in many cases there is more than one purpose

**Luzon et al CPT 2016**
Why a PBPK Guideline?

• Qualification of the intended use is mostly lacking

• The reports of the PBPK simulations do not contain enough details
  – Lack of sensitivity and uncertainty analysis
Qualification of the PBPK platform for the intended use - What do we mean?

Qualification is related to the PBPK platform

- Is there enough scientific support for a certain use for that particular platform?

- **DDI**
  - Enzyme inhibition
  - Induction
  - Transporter

- **IVIVC**

- **Formulation changes**
  - Biowaivers

- **Extrapolation of PK data in young children**

- **Food effects**

- **Prediction of PK in Special populations**
Qualification is important for high regulatory impact decisions

• High regulatory impact decisions

Examples:
» All changes to SmPC (ie label)
» Use of a PBPK model in place of clinical data (DDI, BE study)
» Non studied scenarios
» Extrapolation outside the studied area

• Medium regulatory impact decisions

» Such as paediatric dose setting that will be confirmed by a clinical study
Why do we want to have Qualification?

- Harmonising the assessment of PBPK applications across the European countries

- Presently not all aspects included in PBPK platforms is entirely scientifically justified and not suitable for high regulatory impact decisions

- From our view this is not a restriction/hinder for the development in this area. It is expected to improve the acceptability of the submitted models by EU regulators
The Qualification data set

• Qualification dataset should be pre-specified,

• Selection criteria for the drugs and the \textit{in vitro} and \textit{in vivo} parameters for these drugs should be described.

• The dataset should, if possible, cover a range of pharmacokinetic characteristics, such as permeability, extraction ratio, protein binding etc. that could influence the outcome.

• A restricted dataset could in some cases lead to constraints in the validity of the qualification.
Case example I

• **The intended purpose:** is to predict whether a drug is an *in vivo* CYP3A4 inhibitor in adult healthy subjects based on *in vitro* Ki

• **The qualification of the platform:** should show the capacity to detect the observed *in vivo* inhibitory effect of different inhibitors on sensitive probe substrate(s) for the enzyme in question.

• **Data set:** should include a large number of inhibitors of different potency with both *in vitro* and *in vivo* data.

• If the aim is to qualitatively predict DDI, false negatives, of a perpetrator drug in the dataset, should be addressed, e.g., by sensitivity analysis
Can absorption related PBPK be used to predict the in vivo relevance of formulations?

• Prediction of a drug’s oral absorption characteristics from its formulation requires knowledge on the interplay among physiology, the drug product, and the drug substance.

• Confidence in at present low

• Some GAPs
  – GI physiology factors
  – The confidence in in vitro dissolution data - in vivo profile?
  – Interplay
Examples of factors that could be of importance to consider in a Qualification data set

**Food interaction:**
Predict large number of drugs food interaction

- Solubility
- BCS class
- Intestinal first-pass?
- Fabs?
- Formulation
- Extraction ratio
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