PBPK submissions and review experience in EMA and EMA draft guideline

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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.
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
Increase in PBPK submission to EMA

Luzon et al. 2016 CPT
### Purpose of PBPK models submitted to EMA

<table>
<thead>
<tr>
<th>Main categories</th>
<th>Specific purpose</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intrinsic factors</strong></td>
<td>General description of PK parameters</td>
<td>8</td>
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<tr>
<td></td>
<td>Organ impairment</td>
<td>8</td>
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<tr>
<td></td>
<td>Differences across groups (ethnicity, disease states, age groups)</td>
<td>5</td>
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<tr>
<td></td>
<td>Effect of polymorphisms</td>
<td>7</td>
</tr>
<tr>
<td><strong>Extrinsic factors (interactions)</strong></td>
<td>DDI involving enzymes</td>
<td>37</td>
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<tr>
<td></td>
<td>Drug as victim</td>
<td>23</td>
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<tr>
<td></td>
<td>Drug as perpetrator</td>
<td>3</td>
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<tr>
<td></td>
<td>DDI involving transporters</td>
<td>8</td>
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<tr>
<td></td>
<td>Drug as victim</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Drug as perpetrator</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Food-drug interactions</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Interaction with cigarette smoke</td>
<td>1</td>
</tr>
<tr>
<td><strong>Drug parameters</strong></td>
<td>Comparison between strengths/formulations</td>
<td>8</td>
</tr>
</tbody>
</table>

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
  » Such as waiving for a study
  » Non studied scenarios
  » Extrapolation of pk-information in to younger age groups

• 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
How to Qualify?

1. **Via a CHMP qualification procedure (EMA/CHMP/SAWP/72894/2008/Rev.3).**
   - Will be presented on EMA web site and a reference to this location in a regulatory submission is sufficient. In this case, the qualification can be referred in future applications with the same intended use.

2. **Via a regulatory submission**
   - only valid for that particular submission and need to be resubmitted and re-evaluated in future applications.

3. **In the future, qualification may also be supported by, e.g. learned societies.**
   - In these cases, their qualification report for a specific use of the PBPK platform should be submitted in the submission. The data set and results should be described in sufficient detail to allow a secondary assessment.
   - Should of course fulfill the GL requirements eg on the dataset.

- can include published papers if the included dataset and simulations are described in sufficient detail to allow a secondary assessment.
The Qualification data set

• Qualification dataset should be pre-specified, the same data set irrespective of Qualification process.

• Selection criteria for the drugs and the in vitro and 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.
Case example II

- **The intended purpose:** was to use PBPK to predict the pharmacokinetic of drug X in children below 6 years as the clinical pk data is very limited in this age group.

- **The qualification of the platform:** should show the capacity for this intended use using external/litterature PK data from children at the same age range.

- **Data set:** should be able to predict the pharmacokinetic of compounds metabolised via the same enzymes in children, extraction grade, have similar absorption characteristics etc. as drug X with adequate performance.
Qualification – other aspects

• Verification of the PBPK platform
  – Focused on the correctness of the mathematical model structure. Details of the differential equations used and the parameterisations of the PBPK model needs to be presented.
  – The maintenance of mass-balance as well as blood flow balances within the model should be supported;
  – Equations and parameter values should be devoid of syntax or mathematical errors.
  – It should be ensured that there are no numerical errors

• Installation control
  – The key functionality of the program should be tested in the computing environment
Files supplied in the PBPK platform

• The adequacy of pk of any files (e.g., inhibitors, inducers and probe drugs) used in the simulation needs to be confirmed

In addition:

• For an inhibitor/inducer file; the in vivo effect of inhibition must be well predicted

• For an substrate; fm should be confirmed in vivo
Review Experience in EMA – what is missing from the reports

- **Drug model**
  - Observed vs predicted data
    - AUC and Cmax or R is often used
    - We also would like to see half-life
  - Plasma – concentration time profile
    - Discussion around if the prediction is adequate
    - Capturing variability
Review Experience in EMA – what is missing from the reports

- Generally see a lack of investigation of uncertainty in the model parameters
  - Sensitivity analysis, often needed to assess multiple parameters at the same time
  - Perform for all parameters that are likely to markedly influence the outcome
  - Should discuss the impact
  - Could also include system dependent parameters that are uncertain such as kdeg
Questions please contact: anna.nordmark@mpa.se
Experience, opportunity and challenges in submitting PBPK analyses to regulators and comments to EMA and FDA draft guidance documents

Neil Parrott, Roche Pharma Research and Early Development

A presentation made on behalf of an IQ Working Group at the FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee. March 15, 2017
IQ PBPK Working Group

1. ABBVIE - Robert Carr
2. AGIOS - Kha Le
3. AMGEN - Vijay Upreti
4. ASTELLAS - Christiane Collins
5. ASTRazeneca - Therese Ericsson
6. BMS - Ming Zheng
7. BOEHRINGER-INGELHEIM - Jin Zhou
8. CELGENE - Rangaraj Narayanan
9. EISAI - Edgar Schuck
10. GENENTECH - Yuan Chen
11. GSK - Neil Miller
12. LILLY - Stephen David Hall
13. MERCK SHARP & DOHME - Ying-Hong Wang
14. MERCK SERONO - Sheila-Annie Peters
15. NOVARTIS - Tycho Heimbach
16. PFIZER - Hannah Jones, Susanna.Tse, Theunis Goosens
17. PIERRE-FABRE - Laurence Del Frari
18. ROCHE - Neil Parrott
19. SANOFI - Qiang Lu, Nassim.Djebli
20. SUNOVION - Jing Lin
21. TAKEDA - Natalie Hosea, Mike Zientek
22. UCB - Francois Bouzom
23. VERTEX - Shu-Pei Wu

Timeline
- 21 Jul 16 - EMA draft guidance
- 17 Aug 16 - IQ group kicks off
- 21 Nov 16 - EMA workshop
- 2 Dec 16 - FDA draft guidance
- 31 Jan 17 - Written feedback
- 15 Mar 17 - FDA Advisory Committee Meeting
Overview

• Experience
• Opportunity
• Challenges
• Responses to questions from FDA
• Comments to draft guidance
Industry Experience with PBPK

The opportunities

• Industry work with regulators to enable rapid implementation of aligned and practical guidance for PBPK submissions
• Guidance is sufficiently general and flexible to be applicable given future scientific advances and does not discourage expansion to broader usage
• Guidance helps to align regulatory agencies, pharmaceutical industry, and software vendors to minimize duplicated efforts and ensure that PBPK modelling is optimally leveraged
The opportunities

- Health authority & industry alignment on applications where confidence is high

**Table 1. Confidence, limitations, and challenges for different PBPK applications**

<table>
<thead>
<tr>
<th>Application</th>
<th>Level of confidence</th>
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<tbody>
<tr>
<td>Preclinical and clinical PK prediction</td>
<td>Moderate to high</td>
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<td>CYP cleared substrates</td>
<td></td>
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<tr>
<td>DDI prediction</td>
<td>Moderate to high</td>
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<tr>
<td>Involving reversible CYP inhibition alone or CYP induction alone</td>
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<tr>
<td>Absorption, food effect, and formulation prediction</td>
<td>High</td>
</tr>
<tr>
<td>For high solubility, high permeability compounds (B(DD)CS</td>
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<tr>
<td>Special population PK prediction</td>
<td>Moderate to high</td>
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<tr>
<td>Pharmacogenetics</td>
<td></td>
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<tr>
<td>PBPK-PD prediction and target organ distribution</td>
<td>High</td>
</tr>
<tr>
<td>For small passively permeable molecules</td>
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*Jones et al., CPT 2015, 97(3)*
Challenges

• A rigid guidance could limit applications of PBPK modeling
  • Guidance should not be so specific that it discourages creativity and extensions.
  • Balance the need to define acceptable modeling processes and verification with scope for new applications

• Requirements on individual sponsors for model qualification (and re-qualification) could become so high as to limit usage
  • Efficient collaboration between industry and vendors, with regulatory acknowledgement, must support adequate qualification leading to global acceptance for drug submissions.
Challenges

• The expectations associated with qualification could be different among regulatory agencies.
  • PBPK benefit will be reduced if one agency still requires a clinical study. In consequence investments in modeling will be limited and usage will decline.
  • Ultimately this is to the detriment of optimal drug development since validated PBPK brings efficiency and helps to expose fewer subjects to a compound in development (ethical benefits).
  • A clear consensus on qualification requirements among agencies will promote progress in the use of PBPK in submissions.
Question 1. from FDA

- What information should be included in a physiologically-based pharmacokinetic (PBPK) submission to the FDA to ensure adequacy of an analysis for its intended purpose? Should these recommendations be universal or should there be different recommendations depending on the purpose for which the PBPK submissions will be used (e.g., to inform clinical study planning vs. labeling or regulatory decision making). What are the principles or criteria that should be considered?
How to ensure adequacy for the intended purpose?

• “The level of verification depends on the stage of application, compound properties & importance of dependent decisions”

  Jones et al. CPT 2015, 97(3).

• Key principles:
  • Safety must be maintained (considering patient population)
  • Recognize where science is mature or less mature
  • Assumptions must be clear and should be physiologically sound and consistent with in vivo data.
  • Sensitivity analysis needed for any model inputs/parameters which are relevantly influential
  • Compound models or special population models must be defendable using the supplied documentation or ideally with peer-reviewed publications
Question 2. from FDA

• Based on the proposed workflows described in Figures 2 and 3 as examples, please discuss:
  • a. What criteria should be used to determine that the model is adequately verified for the intended purpose?
  • b. When the model needs modification, what considerations should be given related to modifications of model structure, and/or parameter estimates?
Figure 2 - metabolism DDI

- Validation of CYP3A modulators has been extensive
- However CYP3A is the main drug-metabolizing enzyme and is especially challenging since expression varies enormously among individuals in both liver and gut
- Also same amount of clinical data for validation is simply not available for other enzymes

- We need to build sufficient confidence for other CYPs while recognizing the limitations of available datasets
Proposal: e.g. for a putative CYP2C9 perpetrator

• Need a model for a single validated substrate (e.g. S-warfarin, tobutamide) with high, well-characterized fm for CYP2C9 (>0.9). If hepatic uptake present then extent must be known.

• Use available in vivo data for significant CYP2C9 inhibitors to determine if in vitro Ki predicts in vivo DDIs with the validated substrate.

• If predictions are acceptable (within 2-fold?) then accept predictions for the putative inhibitor on validated substrates.

• Conduct a single clinical study with a well characterized substrate and compare observed to predicted. If acceptable then include predictions for other well-characterized substrates in label.
Proposal: Effect of Inhibitors on a new CYP2C9 victim

• Need a model for a CYP2C9 substrate that includes a well-characterized fm for CYP2C9 and knowledge of the extent of hepatic uptake if present

• Predict DDI caused by validated CYP2C9 inhibitors.

• Conduct a clinical DDI study of the new substrate with strongest selective CYP2C9 inhibitor available.

• If predictions are acceptable (within 2-fold?) then accept predictions for other validated CYP2C9 inhibitors on new substrate and label accordingly.
Figure 3: Mechanistic absorption models

• This is a nice illustration of application of mechanistic absorption modeling when a lot of clinical data are available.

• However, use within companies is mostly at an earlier stage
  • Examples from Jones et al. 2015: i) salt form selection, ii) formulation development, iii) modified release, iv) food & PPI effect

• We need to build more recognition of the potential to address regulatory questions with qualified absorption models leveraging drug specific in vitro data
Proposal: e.g. effect of food

- Clinical reference dataset should cover drugs within the relevant range of properties around the sponsor drug properties (e.g. BCS 1/2)
- Need clinical verified absorption models with a defined set of inputs for reference dataset including biorelevant solubility and in vitro permeability
- Verify predictions for a reference dataset with clinical data
- For lower impact directly predict with the model
- For higher impact verify with clinical data then predict and label for wider use (e.g. different formulation, high fat meal, timing with a meal etc...)
Comments to current draft guidance

• Both agencies are thanked for their efforts to produce helpful guidance documents and for associated workshops/meetings
• There are currently differences between the agencies and we would appreciate efforts to harmonize as fully as possible the qualification expectations
• More discussion of qualification and analysis requirements will be helpful to reach alignment
• Further examples/case studies of applications and qualification that agencies consider to be appropriate would be helpful.