PBPK workshop

Introduction of the PBPK Guideline and expectations of the day.

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Objective of the workshop

To discuss and get feedback on the PBPK guideline

NB! We will not discuss current qualification status of any specific use

Outline

- **Focus of the meeting**
- **Why a PBPK Guideline?**
- **Housekeeping rules**
- **Qualification of the PBPK platform for the intended use**

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

Focus of todays meeting :

- **In session 2 - Qualification of PBPK platform for the intended use**
- **In session 3 - Reporting including evaluation of drug model**

Why a PBPK Guideline?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

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

Draft

Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetic 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

Comments should be provided using this template. The completed comments form should be sent to pkwpsecretariat@ema.europa.eu

Keywords	***pharmacokinetics, modelling, simulation, qualification, predictive performance***

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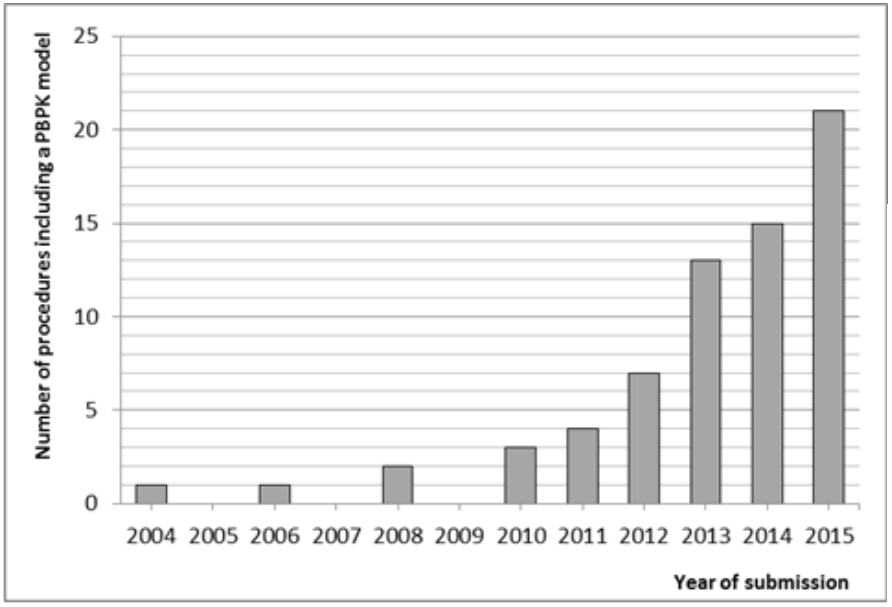
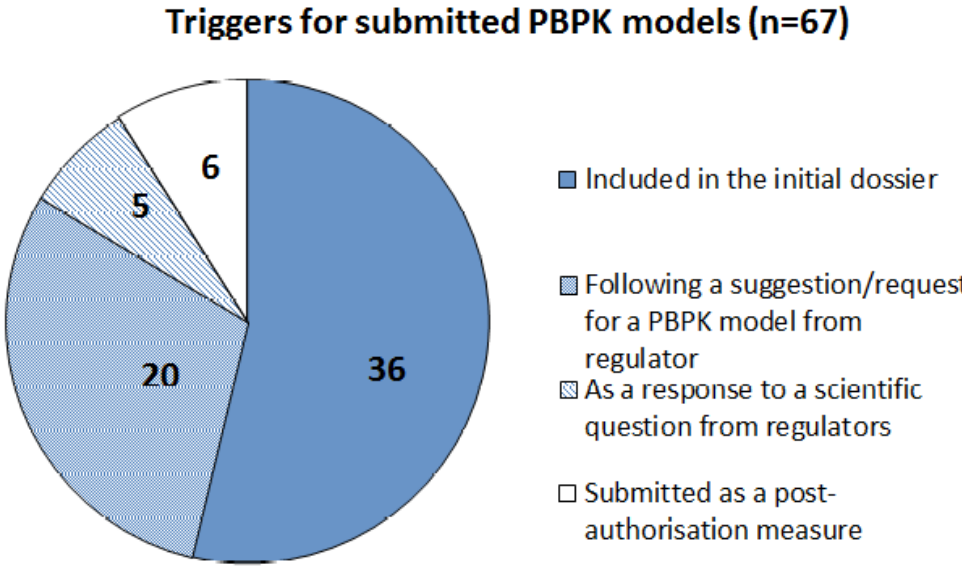
approvals • authorisation • clinical trials • communication • competence • cosmtics • dialogue • directives • efficacy • environment • evaluation • guidelines • harmonisation • health economics • herbals • homeopathics • information • inspection laboratory analysis • market surveillance • medicinal products • medical devices • narcotics • public health • quality• registration • regulations • reliability • risk/benefit • safety • scientific • standardisation • transparency • vigilance • approvals • authorisation • clinical trials • communication • competence • cosmetics • dialogue • directives • efficacy • environment • evaluation • approvals • authorisation • clinical trials • communication • competence • cosmtics • dialogue • directives • efficacy • environment • evaluation • guidelines • harmonisation • health economics • herbals • homeopathics • information • inspection laboratory analysis • market surveillance • medicinal products • medical devices • narcotics • public health •

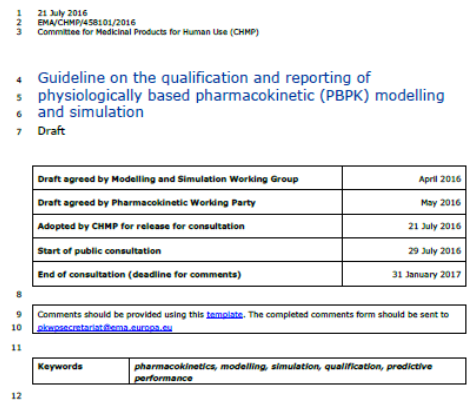
Increase in PBPK submission to EMA





Luzon *et al* 2016 CPT

Why a PBPK Guideline?



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Keywords	*pharmacokinetics, modelling, simulation, qualification, predictive performance*

- **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

Housekeeping rules

- **The focus will be on the guideline and in particular on topics lifted for discussion**
- **An all inclusive discussion atmosphere, everyone's opinion are of importance**

- **The discussion should be scientific/ practical and non-promotional**

Important to remember

- **This meeting is not a replacement of written comments.**
- **Deadline for written comments: 31/01/2017**

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

Reminder

- Specific examples on how to apply this guideline to other applications than DDI of PBPK are not given. The guidance may, however, conceptually be applied when qualifying a PBPK platform for use in any area

- The detailed information in the description of data set is to communicate our current thinking how the data set could be constructed

Aim of this guideline

- **To describe the expected content of PBPK modelling and simulation reports included in regulatory submissions.**
- **To describe the documentation needed to support the qualification of a PBPK platform for an intended use**

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

Extrapolation of PK data in young children

Prediction of Food effect

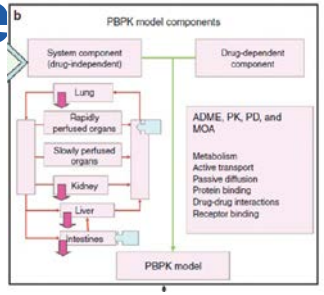
IVIVC

Prediction of PK in Special populations

Formulations changes

Biowaivers

Qualification of the PBPK platform for the intended use- What do we mean?



The Applicant should be able to answer the question :

Has the platform including the specific version been shown to adequately predict the same kind of situations?

This should be evaluated using external data.

- **The extent of qualification required depends on the <u>regulatory</u> impact of the modelling**

Today we will focus on high regulatory impact

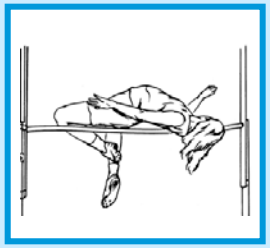
Impact of the M&S exercise on benefit-risk decision and level of regulatory scrutiny

High impact

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

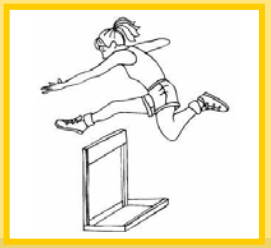
Medium impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } + +



Low impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +



Impact on regulatory decision

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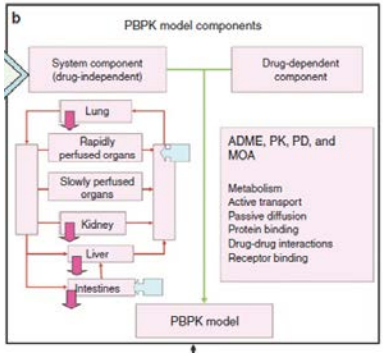
Slide from T. Shepard, 2011

High regulatory impact decisions



- **High regulatory impact decisions**

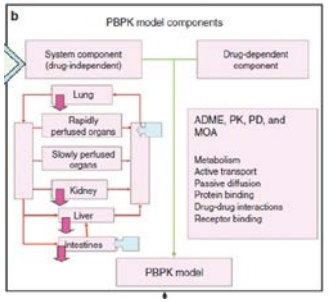
  Examples:

  - » 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 the PBPK platform 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).**

2. **Via a regulatory submission (MAA, type II variation)**

3. **In the future, qualification may also be supported by, e.g. learned societies.**

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

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

The 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

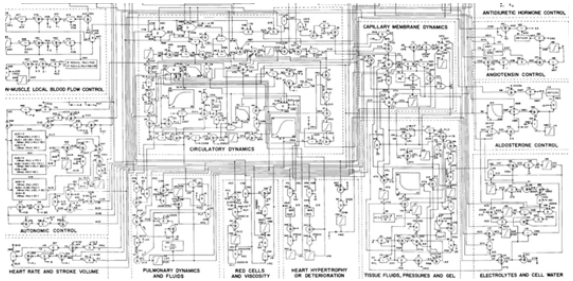
- **The intended purpose:** was to use PBPK to predict the pharmacokinetic of drug X in children as the clinical pk data is very limited in this age group**.**
- **High regulatory impact** : The platform should be qualified for this intended use using external/litterature PK data from children at the same age range
- **Data set:** The used data set should be able to predict the pharmacokinetic of compounds metabolised via the same enzymes, extraction grade, have similar absorption characteristics etc. as drug X with adequate performance.

Case example III

- **Background**: Anticancer drug that is CYP3A and CYP2C9 substrate. DDI data available with a strong CYP3A inhibitor.

- **The intended purpose:** to predict the effect of dual CYP2C9 and CYP3A inhibitors
- **High regulatory impact** : the intended use with the particular software should have been qualified for the intended purpose. Inhibition of CYP3A4 has been qualified with an earlier version of the software (Fahmi,2009).
- The inhibition of sensitive CYP2C9 substrate(s) has not been qualified, ie it has not been shown that platform can adequately predict the same kind of situations using sensitive CYP2C9 substrates. For this, as large dataset as possible is needed

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

Compound files supplied in the PBPK platform

- **The adequacy of pk of any compound 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**

Thank You!

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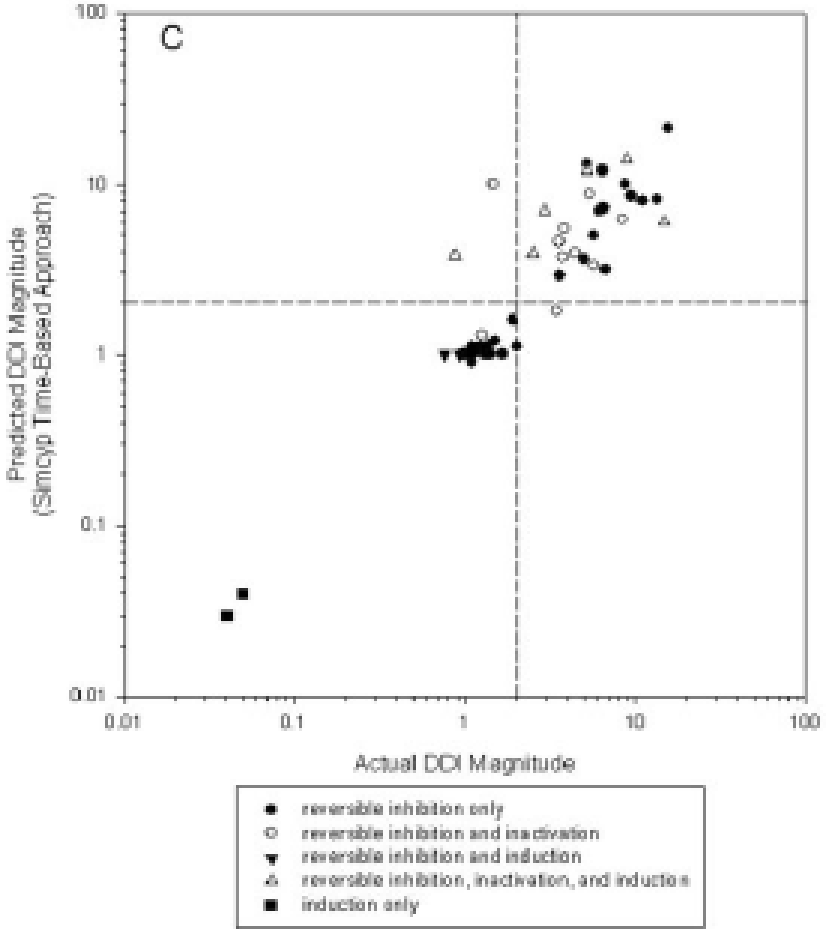
Back up slides



Fahmi DMD 2009

Purpose of PBPK models submitted to EMA

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

up to 31st December 2015*

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

Luzon et al CPT 2016