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

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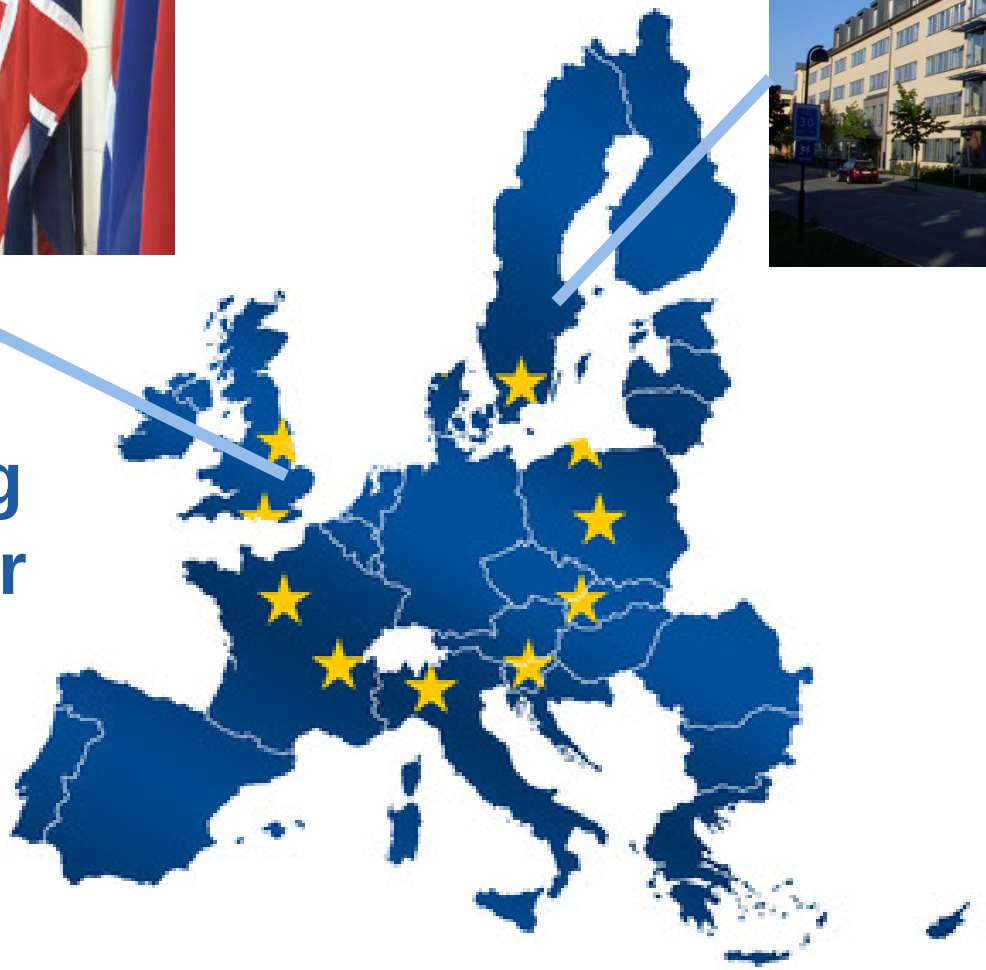
Outline

- **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 : IVIVIC and PBPK

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20 November 2014
EMA/CHMP/EWP/280/96
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)

Draft Agreed by Pharmacokinetics Working Party	October 2012
Adoption by CHMP for release for consultation	21 February 2013
End of consultation (deadline for comments)	15 September 2013
Agreed by Working Party	23 October 2014
Adoption by Committee	20 November 2014
Date for coming into effect	1 June 2015

This guideline replaces Guideline on Modified Release Oral and Transdermal Dosage Forms Section II (Pharmacokinetic and Clinical Evaluation (EMA/CPMP/EWP/280/96 Corr1)

Keywords	*Modified release, prolonged release, delayed release, transdermal drug delivery systems (TDDS), bioequivalence, pharmacokinetics, biowaiver, in vitro dissolution, generics, oral, intramuscular and subcutaneous*

- 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

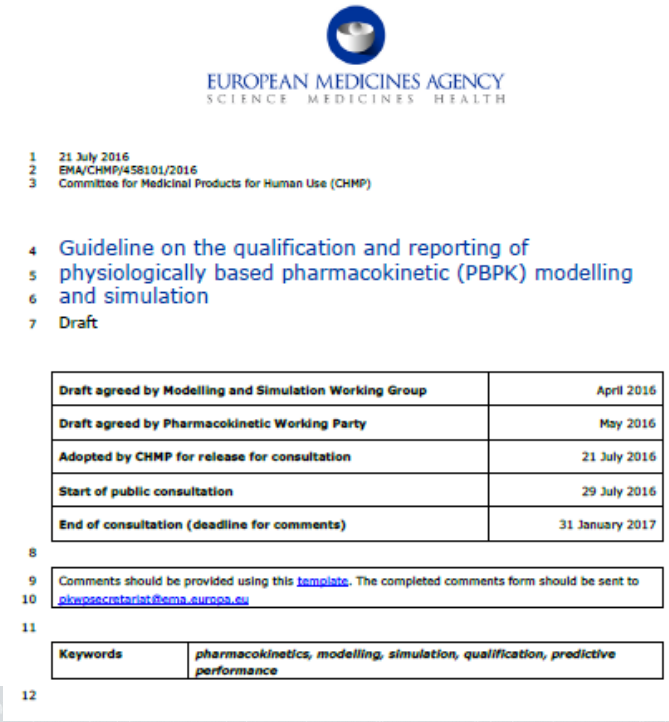
Physiologically Based Pharmacokinetic (PBPK) Modelling and Simulation

Draft was released in July 2016

Public consultation was due 31 Jan 2017

NB! In Europe draft Guidelines are **not**

in to force.



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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

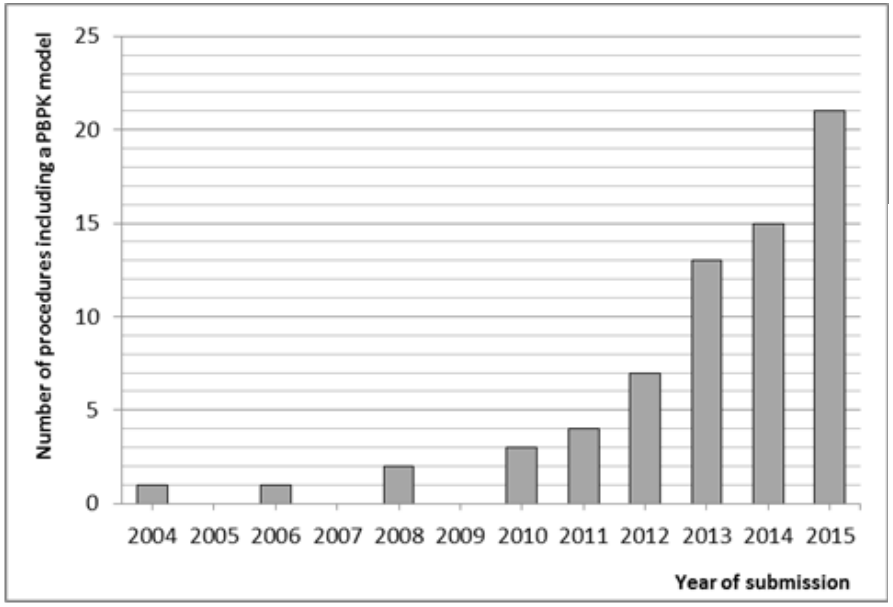
Draft

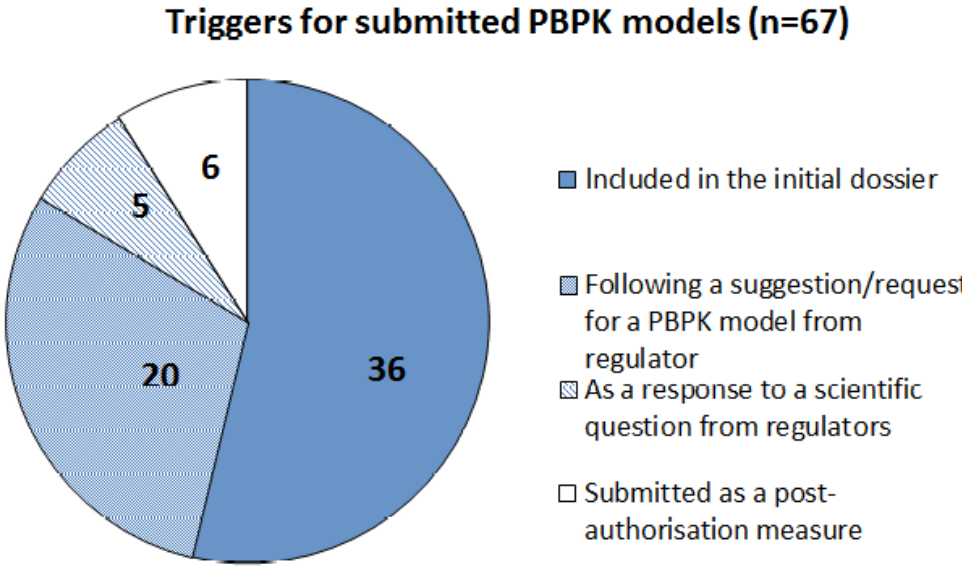
Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetic Working Party	May 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	29 July 2016
End of consultation (deadline for comments)	31 January 2017

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***

Increase in PBPK submission to EMA





Luzon *et al* 2016 CPT

Purpose of PBPK models submitted to EMA

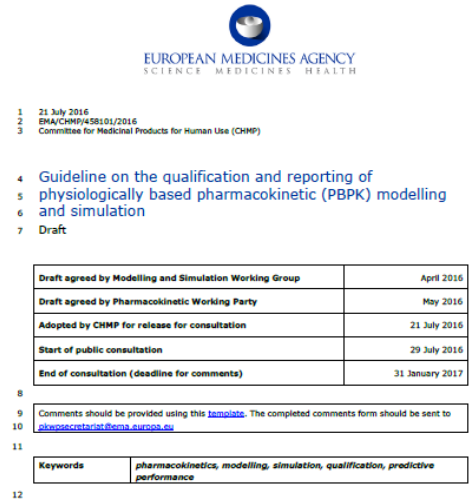
Main categories	Specific purpose		Number
Intrinsic factors	General description of PK parameters		8
	Organ impairment		8
	Differences across groups (ethnicity, disease states, age groups)		5
	Effect of polymorphisms		7
Extrinsic factors (interactions)	DDI involving enzymes	drug as victim	37
		drug as 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

Why a PBPK Guideline?



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- **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

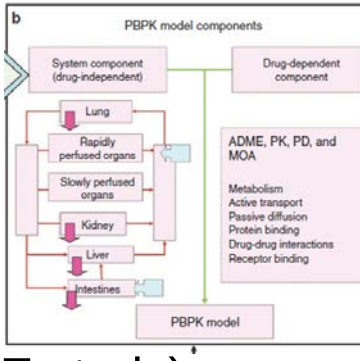
Qualification of the PBPK platform for the intended use- What do we mean?

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**

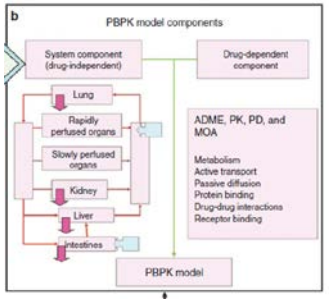
  Examples:

  - » 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 *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

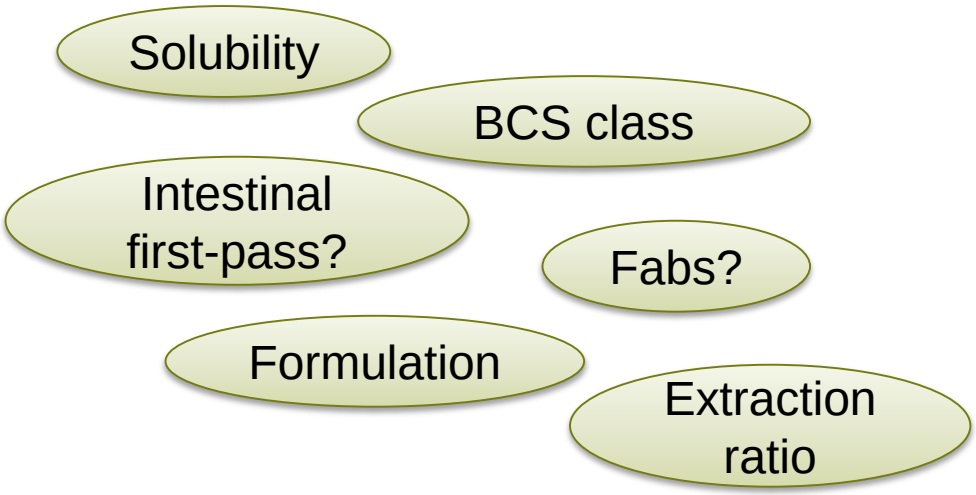
- **The intended purpose:** is to predict whether a drug is an *in vivo* CYP3A4 inhibitor in adult healthy subjects based on in *vitro Ki*
- **The qualification of the platform :** should show the capacity to detect the observed in vivo inhibitory effect of different inhibitors on sensitive probe substrate(s) 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

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



Questions please contact :anna.nordmark@mpa.se

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