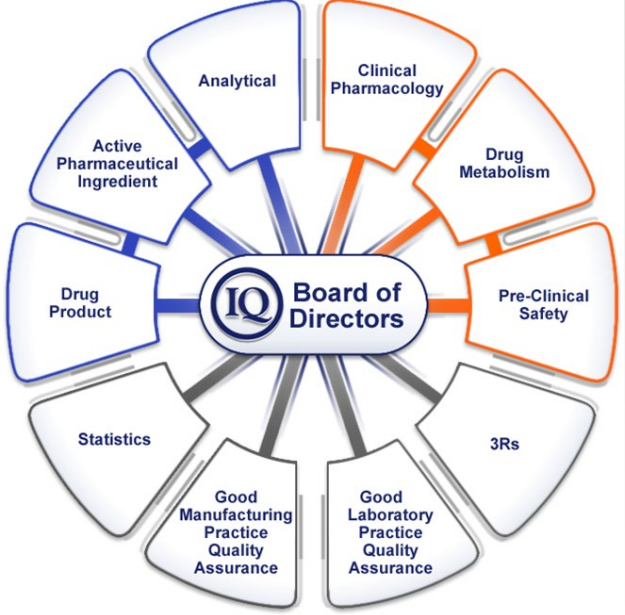
Feedback to the draft guideline on qualification and reporting of PBPK modelling and simulation

A presentation made on behalf of an IQ Working Group at the EMA workshop session on qualification of the PBPK platform for the intended purpose

21 Nov 2016

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



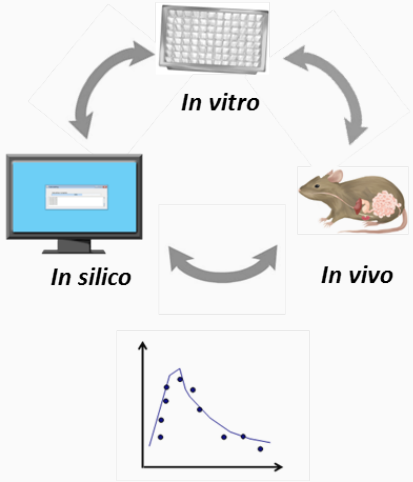
Timeline

- 21 July - EMA release draft
- 17 August - IQ working group kicks off
- Aug through Nov

5 Teleconferences to discuss and align on comments and questions to the document

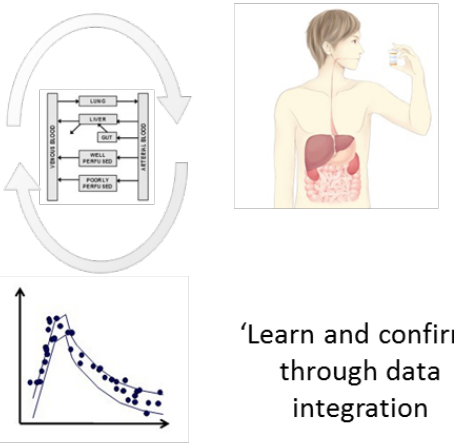
IQ – Industry Perspectives on PBPK

Discovery



**Early risk assessment,
First in human dose projection,
Toxicokinetic dose projection,
Early formulation assessment**

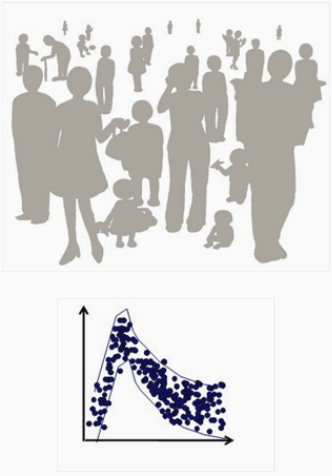
Early Development



'Learn and confirm' through data integration

**First in human, single/multiple ascending dose exposure modeling,
Drug-Drug interaction, Food effect,
Formulation/Absorption modeling
Healthy subjects & patients**

Late Development



**Phase I-IV trials
Patient trials,
Special populations,
Label requirements**

Continuous Model Refinement & Validation

Jones et al. "Physiologically based pharmacokinetic modeling in drug discovery and development: A pharmaceutical industry perspective." Clinical pharmacology & Therapeutics 201597(3): 247-262.

Our Aims

- To provide constructive input to enable a rapid implementation of a practical guidance for PBPK
- To achieve alignment on the roles of regulatory agencies, pharmaceutical industry, and software vendor in the qualification process
- To ensure that the guidance is sufficiently general to be applicable and useful given future scientific advances in PBPK

Question 1: Are the approach of the 3 practical qualification processes adequate? (Please discuss pros and cons of the different processes)

- The 3 processes could be more clearly defined

- CHMP133 qualification procedure
  - Pros: lessens duplication or efforts, simplifies agency review,
  - Cons: unsure how completely & rapidly vendors can do it?
- Within the context of a regulatory submission
  - Pros: not dependent on vendors
  - Cons: encourages duplication of efforts, inconsistency and complicates agency review
- Supported by learned societies
  - Pros: lessens duplication or efforts, simplifies agency review,
  - Cons: how would it happen? Who are the “learned societies” ?

Question 2: Do you agree with the qualification dataset descriptions as outlined in the guideline? (Please discuss)

- Currently outlined as a mixture of generic vs specific. But often very specific to DDI inhibitors
  - Recommend to provide a clearer description of generic requirements for qualification datasets and apply for DDI inhibitors as an illustrative example
- Would be helpful if dataset descriptions in different parts of the document could be consolidated in one place
- Further clarification would be useful
  - What exactly is meant by external data? (e.g. Line 71, 130,..)
  - Clarify requirement of PK characteristics for dataset molecules used in different ways e.g. requirements for perpetrator vs victim drugs (e.g. Line 155-156)
  - Update when agency and industry have gathered experience

Question 3: How would you qualify a PBPK platform for an intended purpose, as outlined in the Guideline? (Preferably with examples). Focus should be on a high impact application.

- Refer to Jones et al. CPT 2015, 97(3).
- Assumptions should be physiologically sound and consistent with in vivo data. Reliable IVIVE must be confirmed.
- The level of verification depends on the stage of application, compound properties, importance of dependent decisions
- Used compound model or special population models must be well verified with supplied documentation or ideally with peer-reviewed publications
- In some cases, the science is not mature enough but several areas showed high confidence

Question 3: How would you qualify a PBPK platform for an intended purpose, as outlined in the Guideline? (Preferably with examples). Focus should be on a high impact application.

Selected PBPK areas of higher confidence from Jones et al., CPT 2015, 97(3)

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

Application		Level of confidence
Preclinical and clinical PK prediction	CYP cleared substrates	Moderate to high
DDI prediction	Involving reversible CYP inhibition alone or CYP induction alone	Moderate to high
Absorption, food effect, and formulation prediction	For high solubility, high permeability compounds (B(DD)CS I drugs)	High
	Pharmacogenetics	Moderate to high
PBPK-PD prediction and target organ distribution	For small passively permeable molecules	High

Question 3: How would you qualify a PBPK platform for an intended purpose, as outlined in the Guideline?

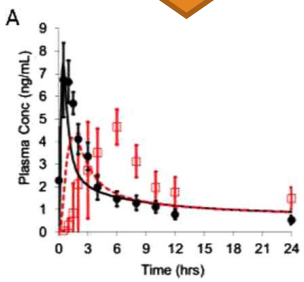
Example of verification and use of compound model for dissolution IVIVC - see Example 1 in Jones et al., CPT 2015, 97(3).

In vitro absorption inputs

Input Parameter	Value
Molecular weight	326
LogD pH 7.4	4.0
Charge/pKa	Base 4.7
Human Peff [* 10E-4 cm/s]	7.5
Phosphate buffer solubility pH 7 [mg/mL]	<0.001
SGF pH 1.4 [mg/mL]	1.67
FaSSIF pH 6.5 [mg/mL]	0.012
FeSSIF pH 5 [mg/mL]	0.135
Clearance in NHP [ml/min/kg]	7
Oral Clearance in human [ml/min/kg]	4.5

PK absorption model qualification:

- Biorelevant solubility => food effect clinical dataset
- in vitro -> Peff dataset
- Dataset should cover relevant range of sol. & Peff around sponsor drug properties



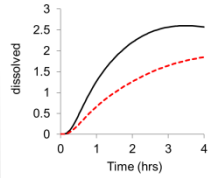
IR PK verification – fed and fasted

Sponsor drug model qualification:

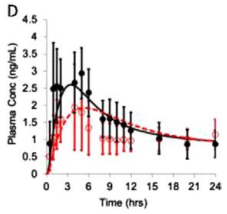
- Supported by pre-clinical data
- Supported by simulations of clinical studies
- Good understanding of PK processes

MR IVIVC verification for sponsor drug

In vitro



In vivo



Impact : IVIVC based on a mechanistic absorption model Surrogate for in vivo bioavailability studies. Biowaivers

See Example 1: Jones et al. CPT 2015, 97(3).

Question 4: In a constructive way - what changes would you propose?

- We recommend a clearer separation within the guidance of the drug dependent & drug independent components.
- When considering implementation of the qualification process and the roles of the software vendor vs the drug application sponsor a clearer separation of drug and system can be helpful.
- More clarity on characterization of site specific enzymatic metabolism/inhibition. How & when?

Question 4: In a constructive way - what changes would you propose?

- We recommend not to require most recent software version (as is strongly suggested in Section 4.4.)
- We feel that if a model in a particular version is deemed qualified then the model should remain qualified for its intended purpose. Release of a new version does not overturn conclusions based on a previous version if that version has been qualified.
- If the intention is to exclude old and obsolete platforms from submission, EMA should rather communicate that older versions are no longer qualified at the point that it is decided they are not valid.
- Systematic re-qualification of all submitted models would become a major overhead and could limit the use of PBPK by sponsors.

Question 4: In a constructive way - what changes would you propose?

- More openness & encouragement for diverse applications
- Clear CYP3A induction without confounding TDI is verified and published (see references below*)
- More mention of absorption modeling e.g. food effect or PPI related drug interactions.
- More examples of diverse application including mechanistic absorption modelling, hepatic or renal impairment, multiple dose prediction from single dose data etc…
- More details on requirements for medium and low impact applications, once relevant experience is gathered

*

- Xu et al., 2011 Drug Metab. Dispos. 39, 1139-48
- Einolf et al. (2014). Clin Pharmacol Ther. 95(2): 179-188
- Wagner et al. Clin Pharmacokinet. 2016;55(4):475-83

Question 4: In a constructive way - what changes would you propose?

- IV data are not always mandatory particularly at earlier stages of development. Non-clinical and clinical oral data can be sufficient.

Example 1
- A BCS 1/2 drug
- Low in vitro and in vivo metabolism
- High bioavailability in animal species
- Good PBPK model simulations of SAD and MAD data with solubility limited exposure well described
- Good simulation of ketoconazole DDI
- (plus ADME study confirming high Fabs%)

Example 2
- Oral dose co-administered with a labelled IV microdose is also often sufficient

- As far as possible harmonize the qualification expectations between the EMA and FDA