MISG New Technologies Forum on Physiologically-based Pharmacokinetic (PBPK) Modelling and Simulation

MHRA, London, 30 June 2014

Contents

List of abbreviations

Abbreviation	Definition
ADME	Absorption, distribution, metabolism and excretion
AUC	Area under the plasma concentration-time curve
BCS	Biopharmaceutics classification system
BSA	Body surface area
CHMP	Committee for medicinal products for human use (Europe)
CI	Confidence interval
CL_{int}	Intrinsic clearance
CL_R	Renal clearance
Cmax	Maximum plasma concentration
CV	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
FDA	Food and Drug Administration (United States)
Fu	Fraction unbound in plasma
IV	Intravenous
IVIVE	In vitro-in vivo extrapolation
K_{deg}	First-order degradation rate constant
Ki	The dissociation constant of an inhibitor
K_{inact}	Rate constant that defines the maximal rate of inactive enzyme formation
MAA	Marketing authorisation application (Europe)
MBDD	Model-based drug development
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
MIDD	Model-informed drug development
MISG	Ministerial industry strategy group
MPA	Medical Products Agency (Sweden)
MPPGL	Microsomal protein per gram of liver
M&S	Modelling and simulation
MSWG	Modelling and simulation working group (EMA, Europe)
NCE	New chemical entity
NDA	New drug application (United States)
OATP	Organic anion-transporting polypeptide
OCP	Office of Clinical Pharmacology (FDA, United States)
PBPK	Physiologically-based pharmacokinetic
PIP	Paediatric investigation plan
PK/PD	Pharmacokinetics/pharmacodynamics
PKWP	Pharmacokinetics working party
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PXR	Pregnane X receptor
RIS	Relative induction score

Abbreviation	Definition
SA	Sensitivity analysis
SAR	Structure activity relationship
SD	Standard deviation
SmPC	Summary of product characteristics
SPA	Special protocol assessment (United States)
TDI	Time dependent inhibition
TI	Therapeutic index
UGT	Uridine diphosphate glucuronosyltransferase
UK	United Kingdom
US	United States
Vss	Volume of distribution at steady state
WB-PBPK	Whole body PBPK modelling

Foreword

The ABPI and MHRA established the Ministerial Industry Strategy Group (MISG) New Technologies Forum in 2007 to provide a platform to horizon scan scientific developments with potential high impact on the regulation of medicines. The meetings aimed to raise awareness and understanding of the topics to advance medicines development, producing future recommendations to support further progress in these areas. Topics explored at previous meetings include regenerative medicine, clinical trial design, early access, biomarkers and personalised medicines.

The Forum meeting on 30 June 2014 was convened to explore Physiologically-Based Pharmacokinetic (PBPK) modelling and simulation and was preceded by extensive preparations to ensure that the discussions started at an advanced level.

Following a productive meeting including global industry, global regulators and academics, we are very pleased to publish this Forum meeting report and it has enabled us to identify substantial areas to follow-up. This Forum, and future meetings and discussions, will support and enhance the development of PBPK modelling and simulation as a tool in drug development for patient benefit.

Stephen Whitehead
ABPI Chief Executive

Ian Hudson
MHRA Chief Executive

1. Introduction

The purpose of PBPK modelling is to aid efficient quantitative mechanistic understanding of pharmacokinetic/pharmacodynamic (PK/PD) behaviour of a drug and metabolites, and subsequently through simulation facilitate improved design of both studies and drug development programs, and to enable decisions to be made, with sufficient confidence, about scenarios that have not been tested experimentally. A major advantage of PBPK models over empirical model descriptions is greater extrapolation power[1]. As fundamental biochemical processes are described, extrapolation (across species, from adults to children, from healthy subjects to those with impaired organ function, from monotherapy to co-administration with drugs interacting with enzymes or transporters) is possible by replacing input parameter values specific to the extrapolation of interest (e.g. tissue blood flow rates and tissue volumes, etc). A second major advantage is the possibility to fill gaps in understanding of biochemical processes in populations of interest (e.g. neonates) by analysis of data from many different compounds.

These advantages and the availability of commercial software systems have led to increasing use of PBPK models in industry. Applications include simulation of first in human studies, drug-drug interactions (DDI), impact of food or formulation changes and extrapolation to different populations (e.g. paediatric, different ethnic groups, smokers, pregnancy, elderly, renal impairment, hepatic impairment)[2]. PBPK models are intended to estimate levels (including target tissues) where few or no data exist. In some extrapolation applications, the PBPK simulations will be superseded by experimental data, while others will be used as a primary or supplementary support to regulatory decisions (e.g. waiving of an in vivo drug-drug interaction study, limited paediatric data, labelling for unstudied drug combinations).

While there is a very active scientific community advancing knowledge and expertise in PBPK, acceptable standards for regulatory applications are not yet fully developed. This forum was organised specifically to address regulatory applications, to take the next step in defining best practice within a regulatory context, facilitating an exchange among scientists from the pharmaceutical industry, software companies, regulatory agencies (European and worldwide) and academia.

The objectives of the meeting were:

- To facilitate common regulatory/industry understanding of the utility of PBPK modelling and simulation in clinical drug development and regulation.
- To raise awareness in the regulatory community of current approaches and applications of PBPK in the industry, including its use for internal decision making

[1] International Programme on Chemical Safety (IPCS), 2010. Characterization and application of physiologically based pharmacokinetic models in risk assessment, World Health Organization, International Programme on Chemical Safety, Geneva, Switzerland. <http://www.who.int/ipcs/methods/ harmonization/areas/pbpk_models.pdf>.

[2] Jones, HM, Chen, Y, Gibson, C, et al. Physiologically Based Pharmacokinetic Modelling in Drug Discovery and Development: A Pharmaceutical Industry Perspective. Submitted to Clin Pharm Ther.

- To help industry to understand the current regulatory perspectives on the use of PBPK modelling approaches in clinical development decision making including drug labelling.
- To facilitate consensus on best practice on the development, qualification, application and reporting of PBPK.
- To inform the development of regulatory guidance on PBPK.

These objectives were written to be ambitious, acknowledging that a single one-day meeting would be broad and scoping in nature and that follow up meetings on specific topics were likely to be identified during the course of the meeting.

The meeting was chaired by Professor Munir Pirmohamed.

Opening remarks

Rob Hemmings (MHRA)

A huge amount has changed in the regulatory environment in the last 10-15 years. Regulators are now more engaged with innovative scientific fields and are working with industry and academia to set expectations as regards to their use in drug development.

Scientific opinions from the European Medicines Agency (EMA) are given by a series of committees, including the Committee for Medicinal Products for Human Use (CHMP), with responsibility for benefit-risk opinions on marketing authorisation applications (MAAs) and to engage in scientific dialogue with drug developers through their Scientific Advice Working Party. A number of other technical and therapy area working parties support the work of CHMP. These include the Pharmacokinetics Working Party (PKWP) and the Modelling and Simulation Working Group (MSWG) who are groups involved in putting together guidance around PBPK modelling. National competent authorities (e.g. Medicinal and Healthcare products Regulatory Agency [MHRA], Medical Products Agency [MPA] etc) provide the membership of these scientific committees and working parties and contribute significantly to the work of the SAWP and the CHMP.

Sponsors can interact with regulatory agencies in several ways; in terms of the MHRA, there are 3 main routes: helplines (e.g. for clinical trial advice), innovation office, scientific advice meetings.

Routes for interactions with the EMA include: innovation task force, scientific advice/protocol assistance, qualification of novel methodology (e.g. to discuss how to qualify novel methods or biomarkers for use in drug development to support regulatory decision making).

PBPK is an excellent example of a topic whereby regulators and drug developers can engage in scientific dialogue to identify additional validation work that needs to be performed and so that these methods find their appropriate place in MAAs.

2. PBPK: within the frame of model-informed drug development

Prof Malcolm Rowland

Modelling and simulation have been evolving for approximately 20 years in industry (earlier in academia). A notable publication in 1991[3] introduced the idea that PK/PD can be incorporated into every stage (pre-clinical to Phase III clinical) of drug development. Since then, while industrial application of PBPK has lagged behind PK/PD modelling in general, the rate of publications on PBPK and its application has increased substantially in recent years[4], due to a combination of progress in improved methods of in vitro-in vivo extrapolation, increased availability of dedicated software platforms, and increasing regulatory receptivity.

In recognition of the increasing potential for modelling to influence the direction of drug development, the term model-based drug development (MBDD) has evolved to model-informed drug development (MIDD).

PBPK models (classed as mechanistic structural models) take into account a wide range of physiological and compound-specific parameters. Notably, they include all tissues within the body with events in each tissue affecting, and in turn being affected by, other tissues (to variable extents), which means that PBPK models can be complex, with potential for factors being highly correlated.

When performing PBPK modelling, key issues that must be considered are:

- Relevance. Are we predicting the relevant concentration-time profile that addresses meaningful clinical questions?
- Identifiability. When updating (estimating) drug related parameter values of the model in light of clinical data the high dimensionality of the model often means that there is an issue of identifiability.
- Plausibility. If several possible combinations of parameter values equally well fit a set of observations, which one should we select?

As local events in tissues generally drive both PK and PD processes, we should be interested in tissue and not just systemic PK profiles. Also, intravenous (IV) data provides an important source of information to aid PBPK model development, avoiding a potential source of non-identifiability commonly seen when oral only data are available.

Future directions for PBPK modelling include: linking plasma and tissue PK events; linking PBPK to mechanistic PD (efficacy and safety); in biologics, extending beyond monoclonal antibodies; expanding routes of administration and dosage forms beyond oral administration; expanding disease states beyond hepatic and renal; undertaking further work on transporters and on extremes of age; and greater integration with genomics.

[3] Peck, C, Benet, LZ, et al. Opportunities for integration of PK/PD/TK in rational drug development, Clin Pharm Ther 51, 467,1991.
[4] Rowland M, Peck C, Tucker, GT. Physiologically based pharmacokinetics: Applications to drug development and regulatory sciences, Ann. Rev. Pharmacol. Toxicol. 51, 45-73, 2011.

Ultimately, prediction of changes in exposure profiles in subgroups, or due to drug interactions or disease, coupled with exposure-response data, needs to be translated into dosage recommendations. This in turn should help to ensure that there is an adequate number of dose strengths to allow for optimal drug therapy.

3. Industry perspectives: the current application of PBPK modelling in drug development

Dr Jan Snoeys (Janssen)

There are two main strategies utilised for PBPK modelling: bottom up (where only in vitro and in silico data, but no observed PK data, are included in the model) and top down (where in addition, observed PK data are used to modify a model or parameter values).

The preference within Janssen is to use the bottom-up approach. The input data used in this approach are compound-specific and system specific; the in vitro data have to be of very good quality. Janssen have validated in vitro assays robustly with known compounds and systems. In addition, the biopharmaceutics classification system (BCS) is used to aid assay selection, and in vitro-in vivo extrapolation (IVIVE) in animals can be a useful tool in setting parameters for the model. IVIVE can be useful to check whether models are robust and predict whether they will be applicable to humans.

Model verification is required to work out the limitations of the models being used, so the models can be used to predict with confidence.

Examples of verification:

- In vitro data verification – prospective simulations have a good predictive/observed correlation so can be useful, for example in the modelling of hepatocyte intrinsic clearance for BCSI/II compounds.
- Physiology and model structure verification – a large compound set can be used to see whether the model works for certain types of compounds and certain types of physiological model, for example in the prediction of volume of distribution at steady state (Vss). Where it doesn't work, try and work out why. This enables limitations to be determined before using it in the clinical setting.

Model optimisation: If the observed versus predicted outcomes are different, the researcher needs to try to work out the cause of any mismatches using sensitivity analyses or parameter optimisation; however retrospective optimisation moves away from the true added value of PBPK. Fortunately, most hypotheses can be tested experimentally.

Key messages:

- The quality of input data is critical.
- Deep scientific insight on limitations/opportunities of the various in vitro and in vivo models combined with appropriate experimental design is key.
- Drug independent system components/virtual populations should be verified with a variety of compounds with a broad range of physicochemical properties.

- PBPK models should be verified with all relevant observed clinical datasets
- The consequences of model optimisation (using clinical data) should be fully understood.
- One should always be mindful of how accurate simulations of unknown clinical scenarios have to be to allow important decision-making.

Post-presentation discussion

The regulators commented that it is uncommon to see the PBPK models being used to push the boundaries of inclusion criteria in Phase II/III trials (e.g. patients with hepatic impairment), to make them more representative of the patient population likely to be prescribed the drug. This would facilitate generation of clinical data in subpopulations that might otherwise be excluded. The industry representatives commented that model outcomes are often used to influence the study design early on, but only in areas where there is the greatest level of confidence, e.g. drug-drug interactions (DDI).

Dr Hannah Jones (Pfizer)

Pfizer use both commercial and in-house PBPK tools in pre-clinical and clinical pharmacology studies. Some applications of PBPK are very well established and are routinely used with high confidence (e.g. first-in-human PK prediction and study design for small molecules, food effect and DDI predictions, and bridging to different populations). Other applications are less well established (e.g. transporter-mediated PK and DDI predictions for small molecules and whole body-PBPK [WB-PBPK] predictions for large molecules).

Two examples were presented; a Japanese bridging model, and an organic anion-transporting polypeptide (OATP) model.

1. Japanese bridging – predicting PK exposure in the Japanese subjects

The Pharmaceuticals and Medical Devices Agency (PMDA) requested a new drug formulation to be developed. PBPK was used to see if an IV PK profile in Japanese subjects could be predicted thereby eliminating/reducing the need for a Phase I study in Japanese subjects.

The model was set up to incorporate the major and minor metabolic routes, uridine diphosphate glucuronosyltransferase (UGT) intrinsic clearance (CLint), UGT2B15 phenotypic distribution for Japanese and Caucasians, and UGT2B15 relative enzyme activities for each phenotype. The simulations predicted that the PK profile in Caucasians and Japanese would be similar. Using these data, the company needed to run only a single dose Phase I cohort prior to starting Phase II/III trials in Japan, which was accepted by the PMDA.

The cross-ethnicity data obtained in the subsequent trial correlated well with the prediction. It was noted that often if the simulation and clinical trial data mismatch, where there are wide inter-individual differences it can be due to low numbers of patients used in the clinical study, rather than an error in the simulation.

2. OATP-mediated PK prediction

A scaling method for OATP PK was developed using 7 literature compounds that were substrates for OATP, together with standard parameters used in PBPK models. When the IV profiles of the 7 literature examples were simulated there was a significant mismatch seen due to an underprediction of the active uptake part of the model, probably due to the substantial differences in the location of the transporter active site between different tissues. This uptake parameter was estimated by fitting the model to develop scaling factors to better match the observed profiles. There were some differences between scaling factors across compounds which need further understanding.

Generic scaling factors were applied to 4 novel compounds to predict human clearance, V_{ss} and the plasma concentration time profile, which were compared to allometric scaling; methodologies. The PBPK methodology gave consistently as good if not better predictions than the allometric scaling; therefore this model has been adopted for use in future projects.

Key messages:

- PBPK tools provide a platform for IVIVE 'learn and confirm' analyses which can be used from discovery to filing
- Models built to describe healthy volunteers can be used to bridge to different populations, although more confidence is required for some populations
- There is still some uncertainty when transporters are involved. The science is less established. DDI predictions can be made at the exploratory level.

Patrice Larger (Novartis)

A wide range of evaluations are supported by PBPK at Novartis: human PK predictions (first-in-human), new populations (e.g. paediatrics), DDI, PK/PD, formulation development, food effect.

Two case examples were presented showing how PBPK modelling could be used to predict the PK in untested populations – pregnancy and paediatrics. The aim of these simulations was to help design studies rather than waiving studies.

1. Pregnancy – Aim: predict exposure and aid dose selection using a simplified pregnancy model

Four reference compounds (3 renally excreted; 1 cytochrome P450 [CYP] 3A4 substrate) were evaluated in a non-pregnancy model (based on PK >6 weeks post-partum) and compared to 2 pregnancy models.

Model 1 – this was built using limited factors (increased body weight, increased cardiac output, CYP3A4 enzyme activity, scaled renal filtration and secretion clearance, and fraction unbound in plasma)

Model 2 – all the factors above, plus increased blood volume, adipose volume, foetal-placental volume, foetal-placental blood flow and enzyme activity.

When the two models were compared, no differences were seen between them. Both predicted equally well the tested renally- and hepatically- (CYP3A4) cleared drugs.

2. Paediatric model – Aim: to decide on a starting dose in a paediatric trial design to avoid overdose

The model was built for a compound in clinical development using available adult male PK data, with modifications for child physiology then applied. Three approaches were used for scaling clearance: body weight scaling, body surface are (BSA) scaling, and inclusion of UGT2BT ontogeny.

When the models were run, large differences were seen when UGT ontogeny was included compared to scaling based on BSA. The most conservative approach (including UGT ontogeny), was therefore used when considering compounds mainly eliminated by UGT.

The actual trial data observed was closer to the BSA-based prediction (with only older children tested at the time of the meeting), but there remains uncertainty as to whether UGT2B7 is the main iso-enzyme for this particular drug; therefore taking the most conservative approach was the appropriate decision. The use of PBPK in this situation allowed several possibilities to be explored.

4. Regulatory perspectives

European Regulatory Perspective: Susan Cole (MHRA), Dr Anna Nordmark (MPA), Dr Ine Rusten (NOMA), Dr Terry Shepard (MHRA)

The EMA regulatory framework views PBPK as a very valuable tool, as evidenced by the recent CHMP concept paper on qualification and reporting of PBPK modelling and analyses, June 2014 (EMA/CHMP/211243/2014) and the mention of PBPK in a variety of other guidelines.[5]

PBPK is viewed as of great potential value to support benefit risk evaluations, providing a mechanistic basis for extrapolation beyond the clinical trial population, reducing uncertainty and enabling better labelling in special populations (e.g. elderly, paediatric, etc). PBPK models can be included in a number of different European procedures including Paediatric Investigation Plans (PIPs), Scientific Advice and MAAs. Data was presented on the current European experience of PBPK applications in each of these submission types.

European regulators view it as the applicant's responsibility to provide high quality documentation supporting the modelling. Modelling is reviewed by relevant experts (e.g., MSWG) acting as an integral part of a multidisciplinary team. Model files are usually requested and used to provide confidence in the decisions being made and as a basis to formulate questions most likely to answer any remaining uncertainties. Opportunities for discussion or clarification of the modelling depend on the particular procedure. Discussion meetings are integral to the EMA qualification procedure and national scientific advice, but are not guaranteed with EMA scientific advice (more likely if a specific question regarding PBPK is included in the advice request). For MAAs, a clarification teleconference can be requested e.g. Day 120.

Three concepts are applied to PBPK modelling and regulatory review: regulatory impact, value and uncertainty (opposite of level of confidence). For medium/high impact (e.g. to support waiver of in vivo study, or to support SmPC statements for drug combinations not tested), it is recommended to seek scientific advice. However, a PBPK application does not need to be of high regulatory impact to be of high value to the drug development programme (e.g. providing quantitative evidence of the plausibility of mechanisms important for the disposition of the drug). Similarly, the level of confidence in a model can be low (e.g. paediatrics), but can still add much value to the programme; in those circumstances uncertainty needs to be managed within the documentation (e.g. by giving plausible ranges around system parameter values that can be utilised to understand the sensitivity of dose recommendations to the inherent model uncertainty).

For verification of drug-specific parameter values, a quantitative understanding of the disposition pathways of the drug based on in vitro and in vivo studies (see slides) and integration across studies, validated with appropriate and convincing in vivo data, is a

[5] Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function (CPMP/EWP/2339/02), Guideline on the investigation of medicinal products in the term and preterm neonate (EMEA/536810/2008), Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev.1 Corr.), Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products (EMA/CHMP/37646/2009)

prerequisite. Other pre-requisites include transparency around uncertainty in the parameter values and understanding and communication of model assumptions. EFPIA are currently considering ways of documenting M&S assumptions as part of the model-informed drug discovery and development (MID3) project.

Companies can seek review of drug models within PIPs, through scientific advice and during MAAs. There may also be circumstances where a Qualification Procedure could be appropriate (e.g. model substrates/inhibitors). System models are normally independent of any particular drug and could ideally suit a Qualification Procedure, where the opinion is published on the EMA website and could be referenced in MAAs, without the need for repeated system model documentation within each drug-specific dossier. Particularly where there is limited confidence in a system model (e.g. paediatric models), documentation of uncertainty in system parameters is important.

'PBPK-thinking' in drug development is encouraged as it leads to a mechanistic understanding of the processes involved in the disposition of a drug, helps to identify gaps in understanding of ADME (i.e. when profiles cannot be predicted), leads to design of more informative studies, reduces the number of uninformative studies, is complementary to other M&S approaches (e.g. to inform dose selection, optimal study design, etc), provides a 'chain of evidence', builds confidence for extrapolation and when systematically applied over many NCEs and many applications supports continued development and validation of system models. This continued development is key to facilitating greater confidence for extrapolation (e.g. paediatric, elderly, DDI, etc), thereby reducing the data requirements in these populations and supporting better drug labelling.

There are particular challenges for qualification of PBPK models that are different from traditional M&S approaches which will require consideration and may benefit from pre-competitive research.

There is now sufficient experience within the European regulatory system to support development of regulatory standards, guidelines and practice. The PBPK concept paper has been published on the EMA website[6] and is open for consultation until the end of September 2014. This meeting is viewed as the beginning of an important dialogue towards defining the standards to facilitate a greater role of PBPK in European regulatory decision making.

Dr Vikram Sinha (FDA)

The Office of Clinical Pharmacology (OCP) at the FDA has observed increasing use of PBPK by drug developers. Between 2008 and 2014, 93 submissions to the FDA contained PBPK modelling, 60 of which were received between 2012 and 2014. The two most frequent uses were in the areas of DDI and paediatrics. Just over a quarter of all PBPK-containing submissions were for oncology.

6 http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500169452&mid=WC0b01ac058009a3dc

The FDA is currently working towards developing best practices and guidance. To this end, 2 workshops have been held this year, one around the use of PBPK in dose selection and the other around the use of PBPK in paediatrics.[7,8]

Based on its review experience, the FDA considers PBPK applications to fall into 3 broad categories, with each consisting of several applications: DDI (e.g. effect of enzyme inhibitor/inducer on substrate PK, effect of investigational drug on the PK of other drugs, transporter DDI); specific populations (e.g. organ impairment and paediatrics); and additional specific populations (e.g. pregnancy, ethnicity, geriatrics, obesity, disease states) and situations (e.g. food effect, formulation change, pH effect, prediction of tissue concentration). Of these applications, two are considered suitable to be used on their own: models of drug as enzyme substrate, and paediatrics over 2 years of age (allometry can also be used). The other applications are not sufficiently developed to be relied upon without other supporting evidence.

When 5 paediatric submissions containing PBPK were looked at in detail, only 3 had used PBPK to predict the starting dose, therefore there is scope for wider use of these methodologies within paediatric programmes.

The FDA will allow the use of PBPK to be represented in the label, where appropriate. For ibrutinib, only actual data for DDI studies including the strong CYP3A inhibitor ketoconazole and strong CYP3A inducer rifampicin were included in the label; representation around moderate inducers and inhibitors in the label originated from simulations. Similarly for ceritinib dose recommendations in the label were proposed based on PBPK simulations.

When submitting PBPK information to the FDA the following need to be provided:

- Summary of model parameter and software
- Logical description of model building and verification process
- Details of simulations
- Model files in an executable format (FDA will often perform a de novo analysis).

Early communication with the agency regarding including the inclusion of PBPK in the development plan is strongly encouraged.

During an NDA review, FDA analysis focusses on the implications for labelling, assessment of unstudied scenarios and consistency in assessments.

Dr Masanobu Sato (PMDA)

The PMDA has seen limited use of PBPK to date.

In September 2013, the PMDA started a new project to look at the evaluation of electronic data including innovative assessment techniques, and this is to include PBPK modelling. The evaluation of electronic data is expected to start in 2016.

[7] http://www.regulations.gov/#!docketBrowser;rpp=25;po=0;dct=N%252BFR%252BPR%252BO;D=FDA-2014-N-0129

[8] http://www.pharmacy.umaryland.edu/centers/cersievents/pediatricpbpk/presentations.html

The Japanese drug interaction guideline is in final draft form (Japanese language only) and this guideline includes PBPK modelling. Similarly to the EMA and FDA, PMDA require sponsors to provide assumptions that are used in the model, evidence of validity of models and simulation results. Analysis of PBPK is not generally viewed as a replacement for observed data in Japan. Results should be checked for consistency with the observed data. If the validity of the model can be explained without contradictions, it may be possible to use the model for other drugs with the same mechanism to reduce the necessity for some types of clinical data.

PMDA is working towards harmonising their guidelines with EMA and FDA guidelines.

The Japanese drug interaction guideline is planning to be finalised and published during Q2 2015, at the earliest.

Post-presentation discussions

When submitting information on a PBPK model to the FDA, whether the OCP will see it depends on when, and by what route, the information is submitted. If information is in briefing documents, the OCP will only get to see it if there is a specific question on that topic. If it is part of an NDA or part of a protocol under special protocol assessment (SPA) then it will automatically be sent to the OCP.

The different regulatory authorities deal with the “black box” commercial software (where the maths is not obvious) in different ways:

MHRA: In the UK and throughout Europe, the regulators do not recommend particular pieces of software, but concentrate more on assessing the basic principles that have been applied.

PMDA: This issue will be considered as part of the project under development.

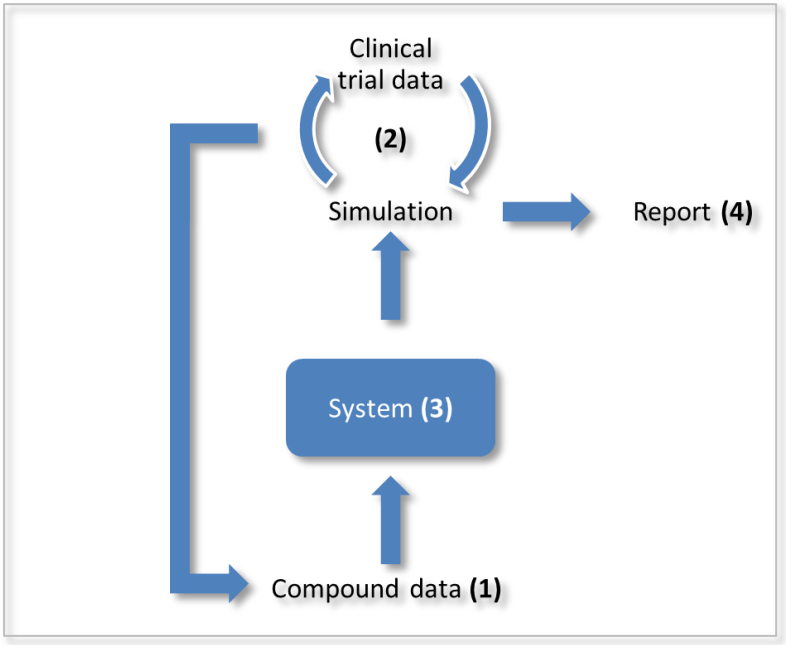
FDA: The regulators in the US do not specify one particular software. Whatever software is chosen, the applicant must be transparent about the parameters entered. FDA can use whatever software they want to in order to verify the results. The main issue is one of software qualification.

5. Discussion topics

5.1. Background

The discussion topics focussed on 4 areas considered to be important in the assessment and reporting of PBPK models:

1. The data input in terms of data specific to the compound of interest.
2. The clinical trial data used to build and qualify the model.
3. The system parameters.
4. Aspects of the report to be submitted to the regulators.



For discussion topics 1, 2 and 4, questions were sent out to delegates prior to the meeting. Anonymised responses to these pre-meeting questions are presented in Appendix 2. Based on the responses received, a list of questions was compiled for further discussion during the meeting.

A summary of the key points and recommendations from each discussion topic can be found in Sections 5.2 to 5.5 below**.** Detailed records of the discussions that took place during the meeting are presented in Appendices 3 to 6.

5.2. Discussion topic 1: What are appropriate data standards for drug input data for PBPK models?

Session led by Dr François Bouzom (Servier) and Ms Susan Cole (MHRA)

Objective of session: To help establish best practice for defining drug-specific input parameters.

Prior to the meeting, a selection of questions were sent to software companies and industry. Based on the responses received, and preferences expressed on the importance of particular questions, a set of questions were put together to be discussed during the meeting. Additional considerations in the selection of the questions were that there appeared to be agreement on the important input parameters and that uncertainty in input parameters and considerations around the lack of IV data would be covered in other discussion sessions.

Anonymised individual responses to the pre-meeting questions can be found in Appendix 2. A summary of pre-meeting responses and further information on question selection can be found in Appendix 3, together with a detailed record of the discussions.

The final set of questions considered at the meeting was:

Question 1: PBPK model improvement during drug development:

- What strategy could be proposed to optimise the input parameters for the study compound that are used as starting points?
- Is there an unacceptable fold change between the initial and the optimised input parameters?
- When are scaling factors acceptable?

Question 2: Which parameters should be included in a sensitivity analysis?

- Definition of a sensitive parameter?

Question 3: Should there be a consensus of methodology?

- It was clear from the feedback received that there is little consensus on the appropriate methodology for determination of key drug input parameters. Should there be an attempt to provide a consensus of methods to be used to determine drug input parameters?

Key points and recommendations from session 1:

Key points:

- Not all parameters are equal - critical values depend on the physicochemical properties of the molecule and on the application or interest (DDI, specific populations such as paediatrics, biopharmaceutics).
- Critical parameters are those that have an impact on addressing clinically relevant questions.
- Depending on the stage of development, in silico values may be useful, but measured values are often preferred. The exception to this is where there is evidence that in silico values are more accurate (e.g., log D for highly lipophilic compounds).
- Methodologies are not consistent across companies or even within some companies. Whilst considered highly desirable, the ideal of a standard in vitro methodology across the industry was not thought to be a realistic aim. Rather, a full understanding and description of methodology with adoption of common reference standards to be utilised across companies should be encouraged.
- It is important to try to understand when poor simulations result from inadequate in vitro data or are due to incomplete understanding of in vivo drug disposition.
- There is mixed acceptance around scaling factors. Physiological scaling factors can be easily accepted e.g. MPPGL (mg of protein per gram of liver), and where a consensus exists would not be expected to be altered. Empirical scaling factors, derived to account for a lack of direct extrapolation from in vitro to in vivo, are likely to be dependent on the in vitro methodology utilised and on the compound, and will be company- or lab-specific.
- Suggested endpoint should be 'Does it modulate dose requirements?'

Recommendations:

- A consensus should be developed on the important input parameters for specific applications e.g. a list of important input parameters for each category (DDI, specific populations, such as paediatrics, biopharmaceutics).
- Guidance on the justification of scaling factors in models should be developed.
- More consideration is required on the incorporation of uncertainty in input parameters in models; consideration of covariance of parameters is also important.
- If companies develop their own scaling factors then they must fully and transparently justify these.
- Agreement and adoption of common reference standards to be utilised across companies should be encouraged.

5.3. Discussion topic 2: Verification of PBPK model parameters for an NCE

Session led by Dr Terry Shepard and Dr Anna Nordmark

Objective of session: To discuss the verification of PBPK models and to explore and define best practice around the use of ADME (in vitro and in vivo) and other in vivo data in the verification of drug-specific input parameters for an NCE.

Prior to the meeting, delegates were provided with 4 examples of PBPK models with high regulatory impact, based on recent submissions to European regulatory agencies (see Appendix 4), and asked to provide feedback in response to a set of questions. The questions below were explored further during the meeting.

Anonymised responses to the pre-meeting questions can be found in Appendix 2. A summary of pre-meeting responses and further information on question selection can be found in Appendix 4, together with detailed record of the discussions.

The final set of questions included in the discussion session are shown below:

Question 1: According to the feedback received, the following points were identified as important to support a quantitative mass balance diagram from Example 2:

- what are the clearance pathways?
- what are their quantitative contributions?
- what is the extent of absorption of the drug and is parent drug in faeces a result of lack of absorption or biliary excretion (fa)?
- what is the extent of first pass metabolism and what are the contributions of intestinal and hepatic first pass loss?
- what is the rate limiting step for hepatic drug clearance (metabolism or uptake)?

Do you agree that these are the necessary questions to answer?

Question 2: The following in vitro studies were identified as part of a clinical pharmacology package supporting the mass balance diagram in Example 2:

- metabolism studies, phenotyping of involved CYPs, in vitro studies with HLM and specific inhibitors
- transporter studies (gut efflux, renal transporters)
- solubility and permeability
- metabolite ID
- plasma protein binding
- blood to plasma ratio.

The following in vivo studies were identified as part of a clinical pharmacology package supporting the mass balance diagram:

- mass balance study PO
- DDI with specific inhibitors (e.g. 2D6, 3A4)
- CYP2D6 PM vs CYP2D6 EM
- IV data
- preclinical ADME with IV and biliary data

- mass balance study IV**.**

Under what specific circumstances could a quantitative mass balance diagram be constructed with confidence, even though IV data are unavailable?

Question 3: The in vitro in vivo extrapolation for induction is different from that of inhibition (Example 1). When a compound is a perpetrator of induction of PXR, the DDI GL in Europe suggests the use of the RIS (relative induction score) method using many calibrators. Are there data to give confidence in the use of a single calibrator for PBPK simulation of induction, particularly where the simulation is to be used to support waiver of an in vivo induction study?

Question 4: What additional analysis is needed under the construction of a PBPK model and during the analysis of for example a drug-drug interaction (Example 3)? How should the range of sensitivity analysis be defined?

Key points and recommendations from session 2:

Key points:

- During drug development, it is best practice to have a quantitative understanding of the contribution of the various pathways involved in a drug's ADME.
- Given the discussion around sensitivity analysis, it would appear that a general guidance could be developed around the choice of parameters and range of values included in sensitivity analysis.
- Although the focus of the discussion was on sensitivity analysis to address input parameter uncertainty, attention should also be paid to the experimental systems themselves and the possibility of improving confidence in key input parameters.
- There are a number of gaps to be filled before PBPK models of enzyme induction will be viewed as sufficiently reliable to support waiver of in vivo studies for a potential perpetrator within the European regulatory system. Further developments in this area would be welcomed.

Recommendations:

- All companies should be encouraged to present "Quantitative Drug Disposition Diagrams" as part of their Clinical Pharmacology documentation.
- A statement should be developed, supported by appropriate rationale that explains the expectation of IV data as a key element in the quantitative mechanistic understanding of drug disposition.
- General guidance should be developed around the choice of parameters and range of values included in sensitivity analysis based on the physicochemical properties of a molecule, and the experimental system utilised (i.e. understanding gained in development of IVIVE, etc).
- Companies should consider whether it is better to resolve uncertainty experimentally where this is possible, rather than addressing this issue solely through sensitivity analysis.

- Companies should systematically document the relationship between in vitro Ki and in vivo DDI results to inform the range for sensitivity analysis for perpetrators.

5.4. Discussion topic 3: Best practice for qualification of system models

Session led by Professor Munir Pirmohamed

Panel: Dr François Bouzom (Servier), Dr Michael Bolger (GastroPlus), Ms Susan Cole (MHRA), Christoph Niederalt (PK-Sim) and Dr Karen Rowland Yeo (SimCYP)

Objective of session: What are reasonable expectations in terms of system qualification?

The session opened with a series of presentations from the 3 software companies: GastroPlus, PK-Sim and SimCYP. Summary slides were then presented to frame the background for the discussion. All 3 companies generally appeared to take similar approaches to validation of their software.

Detailed records of the subsequent discussions are presented in Appendix 5.

GastroPlus (Dr Michael Bolger)

The GastroPlus system is subject to 2 types of qualification (verification): system qualification and libraries qualification.

System qualification comprises 2 main areas:

- Version control systems – tracking changes and revalidation prior to new releases.
- Training data and responsibilities – for each new version release, new tutorials are developed to ensure optimal support for users.

Libraries qualification:

- Physiological parameters included in the software are chosen based on literature review and critical evaluation of the reported values.
- Key parameters depend on modelled drugs on which processes are the most influential in disposition of a given drug in vivo.
- Good default values are used and explanation for their choice is documented; however, it is the responsibility of sponsors to understand the software and not use it in a “black box” fashion.

PK-Sim (Dr Christoph Niederalt)

The PK-Sim software is subject to 3 types of qualification (verification): system qualification, libraries qualification and support simulations qualification.

System qualification:

- Change control – documentation of change requests
- Version control – documentation of software development history
- Validation – comprehensive library of test cases that grows with every new release. There are automatic as well as manual software tests including simulation outputs for standard simulations.

Libraries qualification:

- Databases include physiological and anatomical parameters (taken from libraries/literature)
- Libraries are continuously updated with emerging knowledge
- Projects contain time stamp and version used

Support simulations qualification:

- Responsibilities of software company include -
  - Validation of software
  - Instruction (manual /training)
  - Support (email address)
  - Software tools for drug model evaluation and documentation
- Responsibilities of the user include -
  - Modelling concept including specification of aims, objectives and model evaluation
  - Documentation of assumptions and limitations.

Examples for software tools for drug model evaluation and documentation in PK-Sim: Automatic generation of files with model specification and simulation results as well as model equations and parameters used; history of model development; interface to Matlab and R for customised model analysis in addition to simulation outputs and PK indices generated by PK-Sim.

SimCYP (Dr Karen Rowland Yeo)

The key algorithms used in the SimCYP software are documented and have been published widely in peer reviewed publications to ensure transparency.

In terms of version control, all compound files are run through new versions before release for reassurance around consistency of results from version to version. However, it should be noted that on occasion, compound files may change across versions as more robust data become available and are incorporated.

All software is continuously tested using automated regression testing so performance can be benchmarked.

In addition, SimCYP supply a series of workspace and expected sets so users can verify for themselves that the system is working as expected. For this set of workspaces, the simulations are then compared against known results for performance verification purposes.

Library file qualification: for each compound a file is developed containing key questions to be answered for that particular compound. In vitro data are used where possible within the models, and where there are gaps in the knowledge the files are optimised to fill the gaps. The software provides transparency for the user regarding the source of data or assumptions made within the systems.

With respect to system parameters, key parameters including CYP3A4 enzyme turnover and MPPGL (milligrams of microsomal protein per gram of liver) have been identified and investigated extensively – these results have been peer reviewed and published.

In addition, system parameters for special populations have also been peer reviewed and published. Based on feedback, some of the populations have been refined, for example, paediatrics – this is highlighted in the relevant slide.

Framework to the discussion:

A framework proposed for assessment of systems pharmacology models[9] was circulated in advance of the meeting and used as a starting point for discussion, citing the similarities between PBPK and systems pharmacology models. The framework refers to the US National Academies framework on Validation, Verification and Uncertainty Quantitation[10] . The key elements of the framework are summarised below:

- **Verification**: Software should be "bug-free", with no copying errors. Numerical methods should be verified, and the software should be open access.
- **Validation**: Two types of data should be clearly differentiated and tracked: training data and validation data. Training data should be published with model. Validation data should be novel and varied.
- **Uncertainty**: Uncertainty in model (and input) parameters should be quantified.

Other points of importance that are highlighted in the paper are:

- The models should reflect an understanding of the biological processes.
- Assumptions should be included.
- There is a general need for databases of biological and clinical observations.

The following were discussed during the session:

Question 1: Where are we going in terms of system qualifications?

Question 2: Where are the gaps?

Question 3: What are the potential approaches to fill these gaps?

[9] Understanding the Potential of Systems Pharmacology, unpublished paper written by Gary Mirams (University of Oxford, UK), David Gavaghan (University of Oxford, UK), Mark Davies (AstraZeneca, UK) for the Medical Research Council.

[10] National Research Council. Assessing the Reliability of Complex Models: Mathematical and Statistical Foundations of Verification, Validation, and Uncertainty Quantification. Washington, DC: The National Academies Press, 2012.

Key points and recommendations from the session:

Key points:

- The meeting identified that each software provider has developed internal systems to evaluate and track the reliability of their system models and associated libraries.
- In the field of PBPK, open source software published with the training data sets utilised presents a challenge for software providers wishing to protect their intellectual property. Other solutions, such as open source validation data sets against which commercially available software are validated (for a specific condition of use), could potentially serve the same purpose.
- It was acknowledged that system model qualification is an area that has not been extensively discussed within the PBPK community and that standards are not currently agreed. Further progress to establish best practice is needed.
- There is some mismatch between the terminology used within PBPK and computational science communities: “qualification” or “verification” versus “validation”.

Recommendations

- A working group should be established to compare the use of system model evaluation and assessment terminology in other related fields such as statistics, mathematics and modelling and simulation with the aim of reaching agreement on the terminology and definitions for PBPK.
- A follow up meeting should be convened to address PBPK system model validation and explore solutions (such as open source validation sets), while considering the needs of software companies.

5.5. Discussion topic 4: What should a PBPK report look like?

Session led by Dr Anna Nordmark and Dr Graham Scott

Objective of session: to discuss best practice in PBPK reporting. What information is needed in the report for regulatory review?

Prior to the meeting, a series of questions for discussion 4 were circulated to participants. Anonymised responses to the pre-meeting questions can be found in Appendix 2. Selected questions were chosen for discussion in the meeting.

A summary of pre-meeting responses to all questions can be found in Appendix 6, together with a detailed record of the discussions from the meeting.

The questions chosen for discussion during the meeting were as follows:

Question 5: Model building and verification 'story': Should this be provided? And how detailed should this be?

Question 6: Model verification:

a. Should reports normally include a grid of uncertainty versus sensitivity (as per WHO IPCS publication)? And how could uncertainty be addressed?

b. How best to address plausibility discussions for assumptions included in the model?

c. How much of the report should consider the Therapeutic index and the impact (low medium high as Q 1 above) of the model.

d. Are targets of 0.8 to 1.25 vs. 0.5 to 2.0 helpful? Should they be decided according to the context of the use of the model?

Question 7: Simulations and plots:

a) What range of plots would be best to include in the reports to show predictions and diagnostics?

> **i) Should simulations normally provide geometric means and 90% PIs? Do limitations in the current models preclude the reporting of min and max?**
>
> **ii) Should PK profiles be presented as both log/linear and linear/linear scales?**
>
> **iii) Individual subject concentration data study or mean +/-SD?**

b) How many subjects per trial and how many trials should normally be reported (is the commonly adopted 10x10 about right)?

Key points and recommendations from session 4:

Key points:

Model story

- The model development 'story' should be presented but ought to be fit for purpose and sufficiently detailed to facilitate regulatory review without being overly detailed.
- Development of a PBPK model during a drug development programme can be helpful in promoting a full and integrated understanding of a drug's quantitative disposition. Alongside this overall objective, it is helpful to develop specific plans for the application of PBPK modelling to clinical pharmacology programmes.
- For regulatory submissions it is important to contextualise the purpose of the PBPK model.

Therapeutic index (TI)

- Whether PBPK modelling is used or not, dose adjustment for DDIs or other extrinsic and intrinsic factors should be framed within the context of the TI.
- The acceptability of the PBPK model in terms of targets for successful prediction of clinical data should be interpreted within the context of TI.
-

Recommendations:

- A clear account of the purpose of the modelling effort should be included in the report.
- A fit for purpose model development story should be included in the PBPK report.
- A clear statement of the assumptions underlying the modelling, the input parameters and the relationship of the parameters and the appropriateness of these assumptions, as well as the impact on the predictions, should also be included.
- Relevant targets for successful prediction versus actual clinical data should be set with reference to the TI of the drug.

6. Recommendations

Drug input data

- A consensus should be developed on the important input parameters for specific applications e.g. a list of important input parameters for each category (DDI, specific populations, such as paediatrics, biopharmaceutics).
- Guidance on the justification of scaling factors in models is needed.
- More consideration is required on the incorporation of uncertainty in input parameters in models; consideration of covariance of parameters is also important.
- If companies develop their own scaling factors then they must fully and transparently justify these.
- Agreement and adoption of common reference standards to be utilised across companies should be encouraged.

Verification of PBPK model parameters

- All companies should be encouraged to present “Quantitative Drug Disposition Diagrams” as part of their Clinical Pharmacology documentation.
- A statement should be developed, supported by appropriate rationale that explains the expectation of IV data as a key element in the quantitative mechanistic understanding of drug disposition.
- General guidance should be developed around the choice of parameters and range of values included in sensitivity analysis based on the physicochemical properties of a molecule, and the experimental system utilised (i.e. understanding gained in development of IVIVE, etc).
- Companies should consider whether it is better to resolve uncertainty experimentally where this is possible, rather than addressing this issue solely through sensitivity analysis.
- Companies should systematically document the relationship between in vitro Ki and in vivo DDI results to inform the range for sensitivity analysis for perpetrators.

Qualification of system models

- A working group should be established to compare the use of system model evaluation and assessment terminology in other related fields such as statistics, mathematics and modelling and simulation with the aim of reaching agreement on the terminology and definitions for PBPK.
- A follow up meeting should be convened to address PBPK system model validation and explore solutions (such as open source validation sets), while considering the needs of software companies.

PBPK report

- A clear account of the purpose of the modelling effort should be included in the report.
- A fit for purpose model development story should be included in the PBPK report.

- A clear statement of the assumptions underlying the modelling, the input parameters and the relationship of the parameters and the appropriateness of these assumptions, as well as the impact on the predictions, should also be included.
- Relevant targets for successful prediction versus actual clinical data should be set with reference to the TI of the drug.

APPENDIX 1: Delegate list

First Name	Last Name	Organisation
Jeffrey	Barrett	Sanofi
Michael	Bolger	GastroPlus
Xavier	Boulenc	Sanofi
François	Bouzom	Servier
Marylore	Chenel	Servier
Sue	Cole	MHRA
Claire	Cope	Academy of Medical Sciences
Oscar	Della Pasqua	GSK
Clare	Dixon	CEDIX Medical Writing Ltd
David	Gavaghan	Oxford University
Christopher	Gibson	Merck
Eva	Gil-Berglund	MPA
Stephen	Hall	Lilly
Rob	Hemmings	MHRA
Martin	Hobe	PK-Sim
Ian	Hudson	MHRA
Wilhelm	Huisinga	Potsdam University
Thomas	Jaki	MRC Methodology Hubs
Susanne	Johansson	AstraZeneca
Hannah	Jones	Pfizer
Patrice	Larger	Novartis
Louise	Leong	ABPI
Joerg	Lippert	Bayer
Christian	Luepfert	MerckSerono
Viera	Lukacova	GastroPlus
Scott	Marshall	Pfizer
Jonathan	Mather	BMS
Nick	Meade	Genetic Alliance UK
Christoph	Niederalt	PK-Sim
Anna	Nordmark	MPA
Neil	Parrott	Roche
Munir	Pirmohamed	Liverpool University
Amin	Rostami	Simcyp
Malcolm	Rowland	Manchester University
Karen	Rowland-Yeo	Simcyp
Masanobu	Sato	PMDA
Graham	Scott	Takeda
Terry	Shepard	MHRA
Vikram	Sinha	FDA
Ine	Skottheim-Rusten	NOMA
Jan	Snoeys	Janssen
Dominique	Tytgat	UCB
Piet	Van der Graaf	Leiden University
Stephen	Whitehead	ABPI
Stefan	Willmann	Bayer
Shuying	Yang	GSK
Ping	Zhao	FDA

APPENDIX 2: Individual responses to pre-meeting questions

Discussion 1 responses

	Question	Response
1	Input parameters: a.What are the important input parameters? And for which applications e.g. DDI studies, paediatric or biopharmaceutical studies? b.How can we take into account the uncertainty of these parameters? c.Are there any important or key parameters that are not routinely available within drug development programs that you recommend should be available?	Company 1 b. Sensitivity analysis and simulations of population. Company 2 b. Performing parameter sensitivity analysis and incorporating inter-individual variability or uncertainty into simulations. c. Clinical IV data may be valuable for some questions – this is rarely available. Company 3 b. Sensitivity analysis, this may be for predicted values or within range of uncertainty for measured values. This may center on understanding possible disconnects between predicted and observed data (which parameters may need better definition to improve model). Company 4 Quality of input data is of critical importance for PBPK modelling. Quality implies a good understanding of the assays employed, their reproducibility and typical associated standard errors and the level of IVIVC demonstrated for some reference molecules. The best way to investigate the impact of uncertainty in inputs is via PSA and Monte Carlo simulations. Company 5 - For victim drug (DDI): parameters related to CL part affected by the interaction -For perpetrator (DDI): parameters related to the interaction (Ki, kinact,…) -Paediatric: enzyme isoforms involved (ontogenicity) -biopharmaceutical: all parameters related to solubility and permeability Sensitivity analysis Binding in tissues, in vitro kinetic parameters for parent drug elimination rather than a particular metabolite formation. Company 6 b. The range of literature values for parameters that have been adapted or estimated should be discussed in depth. Company 7 In our experience it is not possible to come to unified list of in vitro input data needed for DDI simulations, paediatric or biopharmaceutical. It depends on the physicochemistry of the drug, how accurate the simulations need to be (therapeutic window + safety of the drug) and if IVIVE observed with available input data and observed PK data and elimination mechanisms in animals and if in vitro animal clearance data can predict in vivo clearance.
2	Is there currently adequate consensus on the appropriate methodology for determination of key input parameters? What are the gaps?	Company 1 No, there is no consensus. Different qualification of in vitro models (reference compounds…). Different results according to the in vitro system used (for fu: dialysis or ultrafiltration – for Clint : recombinant enzymes, microsomes, hepatocytes, S9…). Company 2 All data inputs need to be generated with well validated methodology for which a good understanding of the IVIVC is known. Any gaps are company/institution dependent. Company 3 I do not think there is a unique way of determining parameters. Some assays may need to be acquired in compound specific ways (e.g. most bio-

	Question	Response
		relevant dissolution may not correspond to pharmacopeia methods). In the case of transporters, the gap is not so much in the in-vitro methodology to generate input as in the scaling to physiology (relative expression in-vitro system / in-vivo). Company 4 Although some examples of generation and scaling of metabolism for non-P450s exist this is still an area with a lack of consensus. In the absorption area there is still a lack of consensus over precipitation assays and biorelevant dissolution testing. Company 5 The 'translation' of recombinant isoform data to the in vivo CL (especially when 3A4 is involved). Company 6 No consensus is available. Key input parameters can be experimentally determined in different conditions (in vitro experiments) and/or estimated through QSAR model. The gaps are: systematic under-prediction of metabolic clearance determined in vitro, uncertainty on how to deal with transporter data,… Company 7 Reversible enzyme inhibition, induction in human hepatocytes and MBI seems to generated in consistent way across major Pharma companies. Other parameters (Clint, in vitro binding, transporter data, solubility, permeability, animal distribution data, radiolabelled animal mass balance, etc… not unified across industry)
3	When are *in silico* calculations acceptable? Which parameters and in which setting?	Company 1 We are more confident with physicochemistry parameters (log P, log D), as long as we are not too close to the 'edge' of the correlation if there are fewer molecules or if the assumptions start to 'fall down' like for high logP values in volume of distribution prediction methods. We use fu and BP in silico calculation when no in vitro data available, but we are more confident with in vitro determination. We use in silico calculation for the Kp (not measured). Company 2 In silico data can be used for a range of parameters for applications in early discovery. Tissue Kps will always be predicted using in silico methodology – methodology is well established, measurement of kps in human are not possible and translation from preclinical species may not be relevant. Company 3 Early in development non-measured values may be substituted with predictions / defaults. As compound progresses and applications are more critical, reliable measured values are preferred. Predicted parameters should be checked for plausibility and their sensitivity evaluated. Fg is typically predicted as it can hardly be measured. Similarly, for the determination of the biliary CL the free intracellular concentration is estimated by a calculation. Company 4 In silico estimates can be acceptable if they can be shown to be sufficiently comparable to measurements for the type of molecules under consideration. For both in silico and in vitro inputs IVIVC via PBPK has to be shown for a set of reference molecules. Company 5 Before first in human study, it is unavoidable, with varying success. As much as possible, these estimations should be checked/refined with actual data. Company 6 When? As development step? In silico calculations are acceptable at early stage, as far as the nce is not out of the chemical space used to build up the QSAR model….which is very rarely checked.

	Question	Response
		Company 7 In early phases of discovery and development. If PBPK model outcome is very sensitive to accuracy of these parameters experimental value should be generated
4	Scaling factors: a. When are they acceptable? Where do they come from? b. How can they be qualified and documented? c. Can they be optimised? Acceptable fold change?	Company 1 They come from software who use literature data. Confident with P450 in the liver, less information on P450 in the gut and we are less confident with transporters and other enzymes scaling factor. Confident when they are either measured experimentally (e.g. quantitative protein abundance method) or verified with large datasets of in vivo data. Extrapolation with in vivo data (studies in a large enough population). Optimisation possible especially for transporters. OK for 1.5 fold, acceptable for 2 or 3 fold but for 10 fold: physiological relevance? Reference compound useful to validate this optimisation. Company 2 Scaling factors are acceptable if there is a poor IVIVC, an explanation for the use of the scaling factor and if the scaling factor has been established using a number of other relevant compounds/species. b. Any scaling factors used should be clearly validated and documented. c. An understanding of the rationale for use of a scaling factor should be described to put into context any fold change. Company 3 a. They may be needed when in vitro does not capture adequately in vivo situation. They may be empirical from comparison on in vitro to in vivo for well characterized substances. rCYP450 CLint and transporter CLint are scaled. b. They should be qualified by application for a range of reported compounds. The enzyme / transporter scaling factor should be based on quantitative determination in the respective tissue (data still lacking for some). c. Optimisation should be used with caution with regards to sensitivity and plausibility. Optimisation should have a strong rationale (e.g. different deviating quantification method of abundance determination, which can be demonstrated). Company 4 These are acceptable if they are within the range of uncertainty of the in vitro input. To establish this range requires sufficient data showing IVIVC for reference molecules. They come from model optimisation against in vivo measured data, usually keeping other parameters fixed. In cases where simulated outcomes are highly sensitive to 2 or more uncertain parameters this may exclude a unique solution via optimisation. This uncertainty in the model should be acknowledged and born in mind when using the model for extrapolations. Company 5 For in vitro to in vivo extrapolation. In that case, they come from the literature. For allometry (paediatrics), they could be used down to an age of two. In this case, they are empirical As much as possible, some validation should be performed using analogs They can be optimised (see above). An acceptable fold range will be a case by case. Company 6 For liver transporters they come from hepatocytes in culture versus expressed system with probe compound, as RAF (probe) or REF (protein quantification); this is not ideal because these parameters are rough and assume relative abundance in hepatocytes are the same in vivo. For CYP, we rely on data provided in the softwares. Scaling factors relevance can be tested through sensitivity analysis. Company 7 Dangerous. Can hide absence of crucial input data. Good rationale should exist e.g. on the basis of in vitro animal – in vivo animal extrapolation or in vitro human – in vivo human extrapolation

	Question	Response
5	Definition of a sensitive parameter. Which parameters should be included in a sensitivity analysis? In what applications?	Company 1 A sensitive parameter is a parameter for which a small variation (1% e.g.) results in a "big" impact on AUC or Cmax for example. SA on in vitro parameters or estimated parameters. It depends on the objective of the modelling approach, is safety impact on AUC and C_{max}, if DDI objective impact on AUC ratio. Company 2 A sensitive parameter is a parameter that has a significant effect on the prediction. Parameters included in any sensitivity analysis should be those with some level of uncertainty and key parameters dependent on the modelling question/application. Company 3 Sensitive parameter would be one which value influences notably output. This may be evaluated according to IPCS (p25-26) but interpretation of this may be put in context (use of model, clinical relevance). Parameters which present uncertainty (see point 1) are of special concern; this may also include physiological (structural) parameters. In principal those parameters which demonstrate a high uncertainty and all estimated/assumed parameters. Company 4 Parameters with a high uncertainty should be included. PSA is used to assess the confidence that the model may be used to extrapolate to untested situations. PSA may also guide further work to improve the model by reducing uncertainty in inputs. Company 5 A small change of a sensitive parameter will trigger high change in an output of interest (exposure, half-life, local conc…). Can be important in DDI, paediatric or biopharmaceutical studies. Company 6 In particular at early stages, it depends on the purpose of the model. Generally speaking sensitive analysis should be done with parameters linked to a low level of reliability/ high uncertainty. May be recommendable to perform a sensitivity analysis for every physiological parameter that has been changed from standard setting. Company 7 Depends case by case. At our company, fugut sensitivity analyses for CYP3A DDI simulations is most frequent
6	How could sensitivity analysis be used to address lack of identifiability? (covariance). Please see slides #12-20 of Malcolm Rowland's presentation from the March FDA PBPK workshop (attached).	Company 1 Do sensitivity analysis on output parameters in blood and tissues. Could help to draw hypothesis that could be tested by further in vitro experiments or in vivo study, in order to better understand and manage our compounds in clinic (especially safety and efficacy concern). Then if 2 parameters are shown to vary in the same way during the sensitivity analysis, one may be fixed to a 'plausible' value and the other estimated via parameter estimation or optimisation, rather than estimating both at the same time. Company 2 Sensitivity analysis can be used to explore if there are a single set of values that describe a particular study. However multiple parameters should not be optimised. There must be a clear rationale for any parameter optimisation; the key advantage of PBPK is the mechanistic nature of the modelling so simulations with minimal fitting are preferred. Company 3 Investigate how different parameters influence output in the same direction. Sensitivity analysis on 2 parameters together to find out if more than 1 solution exists that fits observed data. To be applied especially if default modified (top down approach). Plausibility and critical evaluation may still be primary staring point. PBPK is fraught with identifiability issues (numerous parameters) and not all combinations can be

	Question	Response
		tested. Applicability of model to different situations (formulations, populations, study types) may be a more powerful way to evaluate goodness of parameters. <u>Company 4</u> PSA can identify situations where multiple non-unique solutions are possible. Additional data is needed to over come non-identifiability. <u>Company 5</u> Testing different possible scenarios in the sensitivity analysis. Preclinical investigations should be performed to identify the most probable scenario. <u>Company 6</u> Combination of sensitivity analysis toward different parameters should help for identifiability….we have to think over that… <u>Company 7</u> Sensitivity analysis should primary be used for hypotheses generation to drive experiments to evaluate if hypothesis generated by SA is true or not.
7	Model improvement during the drug development: what strategy could be proposed to optimise the input parameters used as starting points? Which parameters? Acceptable fold change?	<u>Company 1</u> Different route of administration or doses should be simulated using the optimised parameter (with a good agreement). In vitro, predicted or in silico parameters. Parameters where the in vitro data is known to be different from the physiological surroundings e.g. aqueous solubility ≠ solubility in the gut. Parameters whose value are fixed within the software to default values but may be sensitive and/or drug-specific (e.g. diffusion layer model parameters for dissolution). Acceptable fold change in the physiological range. <u>Company 2</u> Optimisation of parameters should only be performed if the modification of a particular value can be justified mechanistically e.g. modification of CLint due to common understanding regarding underprediction of CLint. <u>Company 3</u> Detailed mechanistic understanding can be build-in over time (e.g. initial model may only include clearance, final should explain it in terms of enzyme / transporter kinetics …). Similarly bio-pharmaceutics characteristics may be improved other time (dissolution in more bio-relevant media, verification in human studies). Measured values may be substituted to predict ones over time. I do not think there should be a limit in fold change as long as improved values are justified by refined measurements and model verification (e.g. biorelevant solubility may be several fold different from buffer solubility, or indeed predicted values). <u>Company 4</u> Measured data should define the initial ranges of uncertainty for inputs. PSA can then identify the more sensitive parameters and guide further experimentation to reduce these uncertainties. Acceptable fold-changes are based upon the error in the assay used to measure the inputs and on experience of IVIVC for reference molecules. <u>Company 5</u> To generate more in vitro data not only limited to Clint but extended to permeability, transporter involvement… Also, using a similar PBPK model in animals and generating distribution data in tissues. <u>Company 6</u> The refinement of the input parameters depends on the parameters itself. As an example, clearance can be determined with only one time point with liver µsomes at early stage. But, it is surely not enough as the compounds is moving through development step. Therefore, optimisation model is grounded with in vitro improvement parameter and clinical outcomes.

	Question	Response
		Company 7 Depends compound by compound. Use best scientific judgment. Acceptable fold change also depends case by case.
8	How could you mitigate the adverse impact of lack of intravenous data on identifiability of drug input parameters (see slide #19, 20 of Malcolm Rowland's presentation attached above)?	Company 1 To have more information on gut and first pass (in vitro experiments, intestinal microsomes...). To have confidence in prediction of absorption (extent and rate) via preclinical PBPK modelling when IV and PO data are available. Company 2 This is dependent on the question/application. Radiolabelled ADME data may help together with relative bioavailability studies. Company 3 Predict CL from in-vitro / other approaches and verify plausibility. Use absorption model to simulate absorption phase and from this adjust disposition model. Verify plausibility and fit. Company 4 There are cases where the weight of evidence supporting high F% can mitigate against lack of IV data. E.g. high Fabs% shown in mass balance or BCS1 molecule, no relevant metabolism by intestinal enzymes, high F% in pre-clinical species. Company 5 Rowland advised to use iv microdose to refine the PBPK model prior to use oral data. Company 6 For some compounds, lack of IV data is hazardous because some parameters can compensate each other (identifiability). Animal PBPK model (IV and oral) validated with in vivo data should be helpful and used as a golden thread for human situation. Company 7 - For low clearance compounds we have not seen added value of human iv data - For high clearance compounds we have not seen added value of human iv data - For BCSI/BCSII compounds with major CYP3A component in clearance approach was developed to accurately predict human iv clearance For other moderate clearance compounds human iv data can have added value especially if oral PK profile simulations are deviating substantially from observed.

Discussion 2 responses

Example	Question	Response
1.	1. Are the data presented adequately? If not, what else would you expect to be presented?	Company 1 No, we do not feel that the observed or simulated data are presented adequately. The observed and modelled variability on all the data presented in the figure should be included, especially since there was mention of higher than usual variability in the clinical PK for the compound. Since safety issues are anticipated, we also felt it would be useful to look at observed and predicted C_{max} changes (with variability/uncertainty presented). There was very little data presented to discuss how the PBPK model for the victim drug was qualified for the intended use. It would be useful to see the simulated concentration-time profiles (e.g. geomean/median with 10/90 percentiles) for all situations presented in the figure overlaid with individual observed data where appropriate. There should be some data presented to show how the perpetrator PBPK models were qualified and no mention of dose or dose regimen was given. No sensitivity analyses were presented to understand the potential impact of various assumptions on the modelled output. Different absorption models were used with little/no description of what they are and how they may be relevant to the case presented. Company 2 Would like to see the profiles of the observed vs. predicted with and without both keto and the compound in question for verification purposes, the ratios can be deceiving for the drug in question. Would like to see the CIs around the point estimates for the keto study and the prediction intervals around the simulations to get a better idea of the potential variability. Company 3 1. General: besides ratios also important to show data on exposure and PK profile -> to be able to relate to observed clinical exposures and safety 2. Presenting results on prediction of CV% versus observed CV%. 3. The dosing regimen of the inhibitors is useful information Company 4 1. Both absorption models (1 & 2) for Ketoconazole interaction prediction 2. If not presented, visual predictive checks (or at least absolute values for C_{max} & AUC predictions) comparing predicted PK profiles with those observed. 3. Show C_{max} values as well; differences here might indicate transporter involvement 4. 95% confidence intervals for C_{max} and AUC data Company 5 Variability around the shown mean values (observed and simulated) should be provided. Similar to AUC the impact on C_{max} should also be shown. Full details of the PBPK model for the substrate including verification of the model simulations against clinical data. The clinical verification should allow verifying the Fg, Fh and fm CYP3A parameters. This requires clinical data to define the routes of elimination and disposition PK (IV study). Details of what underlies Absorption models 1 & 2. Sensitivity analyses should be done around the key parameters. Validation data for each of the inhibitor models. Either referring to published papers or verification included with the supplied package. Company 6 • Information about variability is missing for both the observations and the prediction. Extreme values are essential for DDI evaluation. • On the graph, it would be useful to represent the different decision making areas, e.g. ratio < 2, 2<ratio<5. Especially the area for which there are potential adverse events. • AUC (± s.d.) of the compound administered alone would be helpful • Information on C_{max} and C_{max} ratio would be useful especially if the effects or adverse events are related to them.

Example	Question	Response
		• 2 different absorption models with no explanation… One would be enough… The best one! And the choice should be documented elsewhere in the report. Company 7 I would expect concentration-time profiles for the predicted DDIs to be presented, especially for the ketoconazole interaction where observed data are available. Because of the large variability observed with the PK, I would expect minimum/maximum AUC ratios or a quantitative measure of the extent of the predicted variability to be presented. In the first instance, there should be an indication of how well the observed variability associated with the ketoconazole DDI is recovered by the model. This would provide some confidence in the predicted variability for the other inhibitors. This is particularly important as safety issues have been flagged with moderate increases in exposure. The fact that there is very little change in half-life but a large increase in AUC indicates that there must be a large change in C_{max} which may add to the safety problem. Thus, prediction of variability is very important. Were changes in C_{max} presented? Company 8 1. What is the effect on C_{max} (the absence of effect on half-life could be a sign of high impact on first pass effect and therefore on C_{max}) 2. What was the predicted and simulated variability in the interaction with ketoconazole (variability is key because expected safety issues with moderate increases in drug exposure)? 3. What is the PK profile of the compound (in the dynamics of the interaction, the extent of the effect will depend on the similarity of the half-lives)?
1.	2. Based on the observed and predicted data, would you be confident in the predictions of the extent of interaction with moderate and weak inhibitors of CYP3A?	Company 1 No, too much information is missing and needs to be clarified. We also think the level at which these issues need addressed is likely dependent upon the intended purpose for the model, which is unclear. For example, if the sponsor is making a case for early inclusion/exclusion criteria from early clinical studies the rigor to which these questions need addressed may be different than if the sponsor was trying to use the model to obtain avoidance for future DDI studies. Company 2 Probably not, depends on what else was submitted with the package we are not seeing. If the modelling depicts the interaction well and the sponsor also can provide the PBPK verification of the other inhibitors (substrate / inhibitor interaction and PK verification). Would need to understand why there is such a difference between strong and moderate/weak inhibitors to provide confidence. The level of confidence in the predictions would also be dependent on the recommendations that arise from results of the DDI studies (see #3). Company 3 1. Is the PK linear in function of time and dose? Evidence for time dependent effects on clearance? Can pathways saturate in function of dose. What was the dose of Compound X used in the keto DDI study and is this exposure still in the linear range when no saturation of non-CYP3A is expected? 2. It should be taken into account that 200mg bid KETO is not completely inhibiting liver CYP3A4, when using this study to estimate fm-cyp3a4. As discussed by Ke et al. (2014), ketoconazole (400 mg qd) results in an AUC ratio of 16.7 for midazolam, itraconazole (200 mg qd) gives an AUCR of 10.8 and clarithromycin (500 mg bid) gives and AUCR of 8.6 on midazolam. In this example 1, AUCR for ketoconazole (200 mg bid) is 27 (so expected to be even higher at 400 mg qd, and itraconazole shows an AUCR of 15 and clarithromycin about 9. 3. How is the contribution of intestinal CYP3A4 vs hepatic CYP3A4 in first pass extraction rationalised and which data are available to give confidence in the simulated fa. 4. Verification of compound files (perpetrator and victim). Can observed clearance be predicted from in vitro intrinsic clearance? Can DDI with 200 mg bid

Example	Question	Response
		ketoconazole be predicted from in vitro data? Or was the observed keto study used to fit the model with several assumptions to come to 27x DDI. 5. Can we exclude significant gut CYP2J2 extraction based on the available preclinical/clinical package? Ketoconazole can substantially inhibit CYP2J2 (e.g. ebastine)? Ketoconazole IC50 for CYP2J2 = 2-5 uM. 6. Can we exclude contribution of esterase based on the available preclinical/clinical package? Ketoconazole IC50 for CES1 = 6 uM. 7. What is the overall safety profile of the compound and efficacy window (high or low therapeutic window) to contextualize the DDI findings Company 4 No: the weak inhibitors show no inhibition at all, the moderate inhibitors show a quite strong effect; this points to an inconsistency. Company 5 Yes - If the additional data specified above was provided. Company 6 To be really confident in the predictions, we need some qualifications: inhibitor predicted concentrations vs observed concentrations, DDI predictions with the same inhibitors and a reference substrate (PK properties as close as possible to those of the studied compound). Company 7 I would be more confident in the predictions of the DDIs if predicted and observed concentration-time profiles for the ketoconazole DDI study were consistent and also changes in C_{max} ratio were presented. In addition, I would like to know that application of the moderate and weak inhibitors for prediction of DDIs with probe CYP3A4 substrates (e.g. midazolam) were successful i.e. that the models had been validated previously. Company 8 To be more confident, we would need more information as the ones mentioned above. A comparison with a substrate similar to the compound and where interaction data in the same condition would be useful.
1.	3. Would you be comfortable to support the team's position that the clinical pharmacology package related to DDI is complete (i.e. using PBPK for extrapolation) ?	Company 1 It depends on what decision is being supported by the model. For early inclusion/exclusion criteria there may be only a little bit of extra information that is needed, for trial avoidance a great deal of additional information would be needed. In general, the information presented is fairly light and does need some follow up. Company 2 Depends on what the label recommendation is. Based on low TI, no other studies with weaker 3A inhibitors and PBPK, I would recommend contraindication with all 3A inhibitors. If the sponsor is willing to take that labeling, then the dataset is complete. If the recommendation is to recommend dosage adjustment for moderate CYP3A inhibitors then more work is needed. Company 3 No. At first sight some worrying observations but depending on the answers to the questions above. At first sight the difference between keto and itra DDI and no effect of mild inhibitors is difficult to rationalize. Company 4 Yes in terms of CYP3A4, evidence that transporters (which were excluded on the previous slide) are not relevant to DDI would be needed. Company 5 Yes - If the additional data specified above was provided and supported that no other enzymes were playing a role in clearance. Company 6

Example	Question	Response
		It would depend on the points mentioned in the questions 1 & 2. Company 7 Not unless the data given in the answers to the previous question were provided. Company 8 Only if no other important pathways (CYP isoforms) are involved in the clearance.
1.	4. If not, what additional studies and/or analyses would you expect to give you the necessary confidence?	Company 1 A study with a moderate inhibitor would provide more confidence, especially since there is a safety issue. Additionally, one could think about whether or not there are any co-meds commonly given in the patient population that may be CYP inhibitors. Company 2 In vivo DDI studies with moderate and possibly weak CYP3A inhibitors. Company 3 See answers to question 2. Company 4 Full in-vitro package would be expected, as well as in-vivo evidence that only CYP3A4 is relevant to DDI: a second in vivo study with a moderate or weak CYP3A inhibitor would strengthen the package, as it could be used as validation of the model Company 5 In vitro data on enzymes involved in metabolism and in vivo metabolite profiles. Company 6 Depending on the qualifications mentioned for the previous questions, an in vivo study with a weak inhibitor could be useful for both the safety issues and the simulation qualifications/optimization. Company 7 I would be more confident in the predictions of the DDI if predicted and observed concentration-time profiles in the absence and presence of ketoconazole were shown to be consistent and also changes in C_{max} ratio were presented. In addition, because of safety issues related to moderate increases in exposure of the drug, a clinical DDI study with a moderate inhibitor may be required to provide the necessary confidence. I would also like to know that application of the moderate and weak inhibitors for prediction of DDIs with probe CYP3A4 substrates (e.g. midazolam) were successful i.e. that the models had been validated previously. Company 8 In vitro investigations to identify all the CYP isoforms involved in the systemic clearance
1.	5. Would the addition of predicted and observed interaction with a strong inducer increase your confidence in the predictions for co-administration of moderate and weak inhibitors of CYP3A?	Company 1 It would add more confidence around the assumption of the fractional CYP3A4-meidated intrinsic clearance (fmCYP3A4), but given the profile of the compound and potential safety issue and study with a moderate/weak inhibitor may be better. Company 2 Inducer study would not significantly increase confidence in inhibition prediction. Company 3 If it can be confirmed that the compound is eliminated by metabolism and the fraction metabolised by CYP3A is derived from the DDI study with ketoconazole and in vitro data, the induction of a strong inducer can be derived as described by Ohno et al. (2007). Ohno et al. published on the basis of more than 40 clinical DDI studies spanning more than 20 CYP3A substrates that if the contribution of CYP3A in the overall clearance of a CYP3A substrate is characterized clinically with a DDI study with a potent CYP3A inhibition, an estimate of the fractional clearance under the control of CYP3A can be obtained. With this estimated value, it is possible to accurately predict the

Example	Question	Response
		decrease in exposure of the CYP3A substrate in the presence of potent and moderate CYP3A inducers if the overall inductive effect of the inducer on liver and intestinal CYP3A is known. Inducers included in this evaluation were rifampin, efavirenz, phenytoin and carbamazepine. Using the approach described by Ohno et al., (2007) for in vivo DDI studies with CYP3A inhibitors and based on the in vivo data available for DDI of ibrutinib with ketoconazole, the relative contribution of CYP3A to the oral clearance (CRCYP3A) can be calculated rearranging the following equation: $$\frac{AUC_{+inhib,oral}}{AUC_{oral}} = \frac{1}{1 - \mathrm{CR_{CYP3A}} * \mathrm{IR_{CYP3A}}}$$ Where IRCYP3A is time-averaged apparent inhibition ratio of CYP3A for an inhibitor (i.e. representing essentially the in vivo inhibition potency of the perpetrator). For ketoconazole the IRCYP3A is 1. As described above, Ohno et al (2008) also derived an equation to calculate the induction potential of a compound, and this calculation is based on inhibition potential of same enzyme: $$\frac{AUC_{+inhib,oral}}{AUC_{oral}} = \frac{1}{1 + \mathrm{CR_{CYP3A}} * \mathrm{IC_{CYP3A}}}$$ Where ICCYP3A is the time-averaged apparent induction ratio (with the same meaning of the above reported inhibitor ratio). For rifampin the ICCYP3A was reported to be 7.7. <u>Company 4</u> Yes, it would support that the chosen CYP3A4 fm is close to in-vivo reality. <u>Company 5</u> Yes – further verification data would help increase confidence. <u>Company 6</u> The only value of this type of study would be a better confidence for the fm value of the substrate. But nothing about the inhibitor potencies and consequently the DDI level. <u>Company 7</u> No. <u>Company 8</u> Could be helpful to have a better idea about the f_m of CYP3A4 but doesn't provide any information regarding the extent of inhibition.
2.	1. What *in vitro and in vivo* studies would you expect to find listed in the Summary of Clinical Pharmacology to support this diagram and give you confidence that the risk assessment is reliable?	<u>Company 1</u>: In vitro data need presented to justify the fractional clearances for CYP3A4 and CYP2D6. Since there appears to be active excretion into the urine, in vitro studies on potential drug transporters should also be presented. A detailed report on the conduct and analysis of the human radiolabelled ADME study should be included. Additional discussion on how to interpret the unchanged drug found in the feces, is it unabsorbed drug or was it excreted into the bile? There may also be preclinical ADME/in vitro data that could help inform on this aspect or possibly a definitive oral bioavailability study in humans. <u>Company 2</u> In vitro: CYP turnover studies for 3A4 and 2D6 (and others); understanding of absorption from in vitro solubility/permeability data; determine kidney transporter involved in active renal excretion. In vivo: Need an IV+PO crossover C14 ADME study to make this diagram. <u>Company 3</u> 1. In vitro phenotyping of involved CYPs. Can in vitro clearance be extrapolated to in vivo? What is the major clearance pathway? What are the rate limiting steps in clearance? (Can hepatic uptake be a rate limiting step?). Do we have clinical study to rationale the contribution of the major clearance pathway in overall clearance in the clinic? E.g. if CYP 2D6 -> can we rationalize contribution of CYP2D6 in overall clearance

Example	Question	Response
		(not present in intestine). E.g. CYP2D6 PM vs CYP2D6 EM or DDI study with specific CYP2D6 inhibitor? If CYP2D6 is major clearance pathways other DDI studies potentially not needed. 2. Are efflux transporters involved in incomplete absorption? E.g. if pgp dual inhibitors of pgp/CYP3A4 can have pronounced effect on PK 3. Is PK linear in function of time? If no -how will relative contribution of pathways shift over time 4. Is PK linear in function of dose? 5. Worst case scenario simulation or observed data? What will happen with potent inhibitors of CYP3A4, and intestinal efflux in CYP2D6 poor metabolisers? 6. In vivo mass balance study. Are the CYP2D6 metabolites structurally different from CYP3A4 metabolites? If yes mass balance has added value on CYP2D6 vs CYP3A4 if no non-linear PK and good recovery of radioactivity + profiled metabolites constitute majority of excreted drug related material. 7. Can we exclude biliary clearance? Depending on the answers above a Fabs study or iv mass balance or combination can have added value or not. <u>Company 4</u> 1. In general in-vivo: human ADME, human DDI studies with CYP3A4 or CYP2D6 inhibitors supporting the fm values concluded from the in vitro phenotyping study, studies including PG on CYP2D6. In general in-vitro: enzyme phenotyping, transporter studies, permeability, solubility 2. Evidence that Fa is really only 50%, rather than parent being found in faeces following biliary excretion (e.g. human IV data, also animal ADME with IV and biliary data) 3. Urinary excretion (clinical: higher than GFR) and transporter (in-vitro) data to substantiate renal elimination statement <u>Company 5</u> In vitro studies with HLM and specific inhibitors to identify CYP metabolism and involved enzymes. IV study to define absolute bioavailability and disposition PK. Mass balance study with radiolabelled compound to measure quantitative elimination in urine and faeces. <u>Company 6</u> In vitro studies to characterize CL, fm, fu and blood to plasma ratio. In vivo studies: IV <u>and</u> oral administration to characterize both the CL and the 1st pass effect + excretion balance study after oral absorption. <u>Company 7</u> I would expect both oral and IV data with both parent and metabolite exposure to be presented. Also, I would expect a mass balance study to be performed with analysis of parent and metabolites in urine and faeces. As CYP3A4 and CYP2D6 contribute to the formation of the metabolites, I would expect *in vitro* data from experiments involving reaction phenotyping or HLM with chemical inhibition or recombinant enzymes to tease out the contributions of the respective enzymes to the overall metabolism. Perhaps clinical studies indicating exposure of parent and metabolites in CYP2D6 EM and PM subjects or DDI studies involving strong CYP3A4 (itraconazole) and CYP2D6 (quinidine) inhibitors. <u>Company 8</u> *In vitro* investigations to identify involved CYP isoforms and respective CL_{int}. Absolute bioavailability study (first pass effect) and ^{14}C ADME study (absorption and excretion).
2.	2. What specific studies would	<u>Company 1</u> In vitro studies using ISEF/RAF calibrated rCYP intrinsic clearance would help or more traditional reaction phenotyping studies (using chemical inhibitors and/or selective

Example	Question	Response
	give you confidence in the partitioning of hepatic clearance across different CYP pathways?	mAbs) could also inform if done in a quantitative manner. Metabolite profiling data from the different enzymes and in vitro systems (liver microsomes and hepatocytes) would also provide supporting data. Company 2 DDI or PgX studies would be best. In vitro metabolism can be used if the findings between in vitro and the C14 studies are consistent. Company 3 1. PK study in EM and PM CYP2D6 metabolisers or CYP2D6 DDI study if evidence that CYP2D6 is major 2. If CYP3A4 is major clearance pathway Fg, Fh need to be rationalized. 3. Are we sure that 50% of drug in unabsorbed and not coming from biliary clearance -> huge impact on DDI predictions with CYP inhibitors. 4. Hepatic uptake rate limiting step? 5. In summary. Major systemic clearance pathway has to be rationalized (renal clearance vs biliary clearance vs CYP3A4 liver vs CYP2D6 liver). Depending on the specifics of the compound needed clinical studies can differ case by case. Company 4 1. In-vitro CYP phenotyping 2. Human AME data 3. Drug interaction studies (inhibition/induction of mentioned pathways) 4. Pharmacogenomics (for polymorphic CYPs: CYP2D6) in phase 1 studies or as popPK co-variate Company 5 DDI study with a specific CYP3A inhibitor to refine fm CYP3A. And/or Study with CYP3D genetic polymorphism populations to refine fm CYP2D6. Company 6 Study with both poor and extensive 2D6 metabolisers. Study with specific inhibitors against 2D6 and/or 3A4. Company 7 As CYP3A4 and CYP2D6 contribute to the formation of the metabolites, I would expect *in vitro* data from experiments involving reaction phenotyping or HLM with chemical inhibition or recombinant enzymes to tease out the contributions of the respective enzymes to the overall metabolism. Perhaps clinical studies indicating exposure of parent and metabolites in CYP2D6 EM and PM subjects or DDI studies involving strong CYP3A4 (itraconazole) and CYP2D6 (quinidine) inhibitors. Company 8 Studies with CYP3A4 and/or CYP2D6 inhibitor A study with poor and extensive metabolizers
3.	1. What sensitivity analysis is crucial for this simulation?	Company 1 We think a sensitivity analysis on the Ki and fu,p would be particularly informative for this simulation. Company 2 Sensitivity analyses for Ki over a dose range is needed Company 3 1. Crucial for this exercise is the confidence you can built on simulating intra enterocyte concentrations and intra hepatocyte concentrations. 2. Fugut = 1 needs to be taken unless available data can rationalize a lower fugut. 3. Can you predict in vivo liver clearance from in vitro liver clearance and in vitro binding? If yes high confidence that liver concentration exposed to liver CYP3A4 is correctly captured. If not is compound hepatic uptake substrate? Has compound high

Example	Question	Response
		permeability? Is the compound extensively ionized base or extensively ionized acid? Is compound extensively bound to plasma proteins? If yes are we sure that only free concentration is driving clearance? Is Ki corrected for binding? Is the compound a lipophilic base with high pKa (> 8.5) (fluvoxamine, fluoxetine like)? If yes connecting in vitro unbound Ki with free plasma concentration without safety factor can result in false negative prediction. 4. Intraenterocyte concentration? Fugut =1 as starting point. Rapidly absorbed drug with potential higher hepatic inlet concentrations? Is PK profile of the compound simulated correctly? Can Fg of compound be simulated well based on ClintCYP3A4, intestinal abundance and fugut? 5. IC50/2 used to estimate Ki? 6. IC50 generated in which model? Is that model extensively verified with control compounds that in vitro conditions generate IC50 value which can be extrapolated to in vivo. <u>Company 4:</u> Influence of Ki changes, fu,mic in inhibition exp., permeability (absorption rate confirmed with clinical data), effect on gut and liver 3A4 <u>Company 5</u> Sensitivity to Ki. <u>Company 6</u> Unbound fractions in plasma and microsomes/hepatocytes Kp liver and Ki Sensitive parameters for the inhibitor predicted concentrations (CL, absorption …) depending on the qualification of the model. <u>Company 7</u> A sensitivity analysis around Ki corrected for non-specific microsomal binding. <u>Company 8</u> Sensitivity analysis on K_i
3.	2. Based on rat QWBA data it is suggested that there is higher liver concentration compared to blood. Will that impact the analysis you would expect to see and if so, how?	<u>Company 1</u> One could compare the predicted liver: blood partition ratio (Kp) to what was observed from rat QWBA. If they are different, the observed Kp value could be used to simulate the anticipated human PK. This may affect the result of the simulation only if it violates the assumption that it is the unbound venous drug concentration driving the effect (i.e. there may be active hepatic uptake). We are mindful that QWBA data represented total radioactivity only, which may be both parent drug and metabolites. As such, those QWBA data should be interpreted accordingly. <u>Company 2</u> Rat liver WBA data is not useful for this analysis. But if we had human in vitro uptake transporter data showing the drug is a good substrate for a liver transporter that should be more of a consideration. <u>Company 3</u> See item 3 above. E.g. if compound if lysosomal trapper or potential hepatic uptake substrate. Especially important if clearance of the compound cannot be predicted based on in vitro clearance data only. <u>Company 4</u> 1. High tissue concentration does not necessarily represent high unbound concentration – Liver tissue binding can be determined in-vitro 2. First evaluate if high liver concentration predicted by PBPK model (if yes, model valid in that respect) 3. Secondly, is QWBA suggesting high concentration during oral absorption? If yes, is this expected in human (fast absorption), does PBPK predict it? Compare to liver inlet concentration estimation 4. QWBA data may represent metabolites as well as parent drug, it may not be directly relevant - Contribution of parent / metabolites may be evaluated in the rat

Example	Question	Response
		Company 5 Higher total liver conc. in rat does not on its own support hepatic uptake. However if there is suspicion of hepatic uptake then the IC50 in microsomes may further under estimate in vivo inhibition implying extra caution in the PBPK model results. Company 6 Not really because QWBA studies deals with radioactive compounds (unchanged compound + metabolites) and there are performed in rats (different hepatic enzymes and transporters). Company 7 Yes this will impact the analysis. If the exposure of the drug is higher in liver than in blood, the predicted degree of inhibition is likely to be higher. Company 8 The higher liver concentration in QWBA study could be explained by metabolites as well. An in vitro study on uptake transporters would be helpful.
3.	3. If the drug also shows TDI for CYP3A, will that influence your confidence in the model predictions?	Company 1 Yes, they would all need to be repeated Company 2 If the drug has TDI and this information is not incorporated into the model, the confidence in the model would decrease. If the TDI information is incorporated into the model, this would increase the confidence in the model however in vitro to in vivo TDI predictions add a layer of complexity to the DDI prediction. Many times phase I midazolam data will help verify the simulation and PK. Company 3 If compound is also CYP3A4 substrate and CYP3A contribution in overall clearance is well characterized multiple dose PK can be very informative (auto inhibition seen?) to verify autoinhibition or induction. Hepatocyte induction data available? Ki kinact assay verified with control compounds? Is TDI coming from inactivation of CYP or from metabolite generating reversible inhibition on CYP3A4? Company 4 1. Yes, impact of TDI after repeated doses would need to be specifically modelled – single dose predictions would still be valid 2. TDI was not included in the model so far and as a consequence the model will not predict its effect. A possible auto-inhibition effect will not be reflected either Company 5 Yes. Validation of PBPK prediction of TDI from in vitro data is less certain than competitive inhibition. Company 6 TDI is very important for repeated administrations. Moreover the prediction of TDI from in vitro data is still tricky and consequently needs additional qualification with reference compound(s) – in vivo data in literature – showing comparable in vitro potency in the same system. Company 7 It depends on whether the inactivation data indicate that it is a weak, moderate or potent TDI. Also it depends on how the inactivation parameters were derived. Company 8 The confidence in the model will decrease, especially for prediction of repeat dose.
4.	1. What are you comfortable to predict using PBPK for	Company 1 We would be comfortable using the model to help mechanistically explain the impact of various intrinsic/extrinsic factors between the studied populations but not comfortable using it to extrapolate to a new population.

Example	Question	Response
	this drug?	Company 2 Would need to have in vitro 3A4 data and in vitro OATP data (and an understanding of the IVIVC of such data with some known OATP substrates) and other standard PBPK inputs – would use this information to predict the human PK profile… However because of the uncertainty in such predictions involving transporters you would need clinical data to verify the model. DDI simulations could then be performed as a follow up once model verification was achieved but would not substitute a DDI study. Company 3 Internally several examples with these characteristics and used to design combination regimens with optimal PK (plasma and liver) parameters proactively. Optimal Fabs design. Optimal DDI designs. Bridge between ethnic groups. Explain PK in patients vs healthy. Bridge from healthy volunteer DDI potential to patient DDI potential. Explain PGx data on OATP polymorphisms. Company 4 1) Moderate confidence in 3A4 metabolism (good characterization needed for non-linearity) 2) Limited confidence for transporter a) More confidence in Km estimation and possible impact in non-linearity b) Less in transporter expression / Vmax 3) Rate limiting step in hepatic elimination (metabolism / transporter) could be investigated in-vitro to inform model Company 5 If the PBPK model predicts the non-linearity seen in vivo but is not able to separate saturation of uptake vs metabolism then it could still be useful for purposes which do not depend on this detail. E.g formulation changes or renal transporter inhibition. Company 6 Not really comfortable with that kind of drug because both the transporter and the enzyme play a role in the clearance and the non linearity. Company 7 In my view, it is difficult to answer this question unless more detail is provided. For example, how was the fmCYP3A4 data derived? What OATP1B1 data are available? In order to try to recover the nonlinearity, full kinetic data (V_{max}/J_{max} and K_m) for CYP3A4 and OATP1B1 are required in the first instance. Company 8 No, because both transporter and enzyme might be involved in the non-linearity. Some clinical information are needed to verify and refine the model
4.	2. For simulations with high regulatory impact (e.g. waiving an *in vivo* study) what additional data would you like to see?	Company 1 There may not be much more in vitro data that would help. Enzyme kinetics for CYP3A4 may help but the biggest concern we have is around the translation of in vitro transporter kinetic data to the in vivo situation. The science is just not quite mature enough. Company 2 It'd probably be good to have two DDI studies done to confirm modelling (1)-itraconazole for 3A and (2)-single dose rifampin for OATP. Then refine the model and predict everything else. These would be needed to tease apart this complex DDI. Company 3 As perpetrator or as victim? Therapeutic/safety window of the drug? Depending on the compound – case by case – variable confidence and experience across industry. E.g. published output in the field currently on IVIVE of OATP substrates e.g. repaglinide, statins… is very variable. Scaling factors needed depending on the compound is mentioned in several publications, other publications mention good IVIVE of hepatic uptake in suspension. Mechanistic modelling of in vitro uptake data needed?

Example	Question	Response
		How to address passive permeability? Can limited permeability of one single cell model be extrapolated to passive permeability in vivo in different organs? In general status of the field can be summarized that there is not Industry/academic consensus on best in vitro model and approach to use for OATP substrates which gives good IVIVE of OATP substrates without need for compound specific scaling factors. In absence of this high regulatory impact is not expected in absence of clinical DDI data. If PBPK model is verified with CYP3A/OATP perpetrators or OATP1B polymorphism data extrapolation to moderate mild perpetrators is possible if confidence can be built that non-linear PK is mechanistically built in correctly in the model. Company 4 1. If available, metabolite data at different doses could help to more confidently establish role of 3A4 in elimination / non-linearity (and relate to in-vitro) 2. Evidence for scaling OATP1B1 data from specific in-vitro system to human in-vivo situation via PBPK (e.g. known substrates with human PK data) or perform a DDI study with an OATP1B1 inhibitor 3. Evidence that no other mechanisms are involved (e.g. intestinal efflux, other transporters involved in elimination) Company 5 In vitro studies to measure V_{max}. K_m for CYP3A and obtain parameters for hepatic uptake (e.g. SCHH studies) Clinical studies in with specific CYP3A inhibitors and OATP1B1 inhibitors (e.g. gemfibrozil and/or rifampin). Company 6 V_{max} and K_m for both the enzyme and the transporter (with reference compounds for the different in vitro tools). The balance between the 2 processes could lead to different strategies to preserve the safety. A mechanistic model including the in vitro data and describing the hepatocyte functioning (influx, passive permeability, metabolism). Again a reference compound with both in vitro and in vivo data is needed to qualify the approach and to increase the confidence in the predictions. Extreme values (C_{max}, AUC) compared to safety data/margins Company 7 I am not sure which data are available so it is not possible to answer this question. Company 8 *In vitro* kinetic parameters (K_m and V_{max}) for both transporter and enzyme. Validation of the model with other compounds with *in vitro* kinetics and clinical data available.

Discussion 4 responses

Question	Question	Response
1	How should the purpose of the modelling effort best be framed? Is the high, medium, low impact paradigm adopted by regulatory agencies useful? (e.g. high impact could mean simulation used to replace a study, medium to justify trial designs and low for internal decision making)	Company 1 Modelling can also be exploratory and used as a learning exercise and to generate ideas. However for support of decisions and for regulatory interactions the purpose should be defined very specifically and clearly. Getting this clear is essential to productive interactions between the sponsor and the HA. Company 2 The classification can be useful. It allows to put modelling effort into perspective of potential impact on human subjects. Company 3 Aim and purpose of modelling should be clearly described together with impact on decision making. Do not completely agree with high, medium, low impact paradigm – internal decision making may still be relatively high impact to the program. What one may find is that the ability to model may vary with the circumstances. Thus, while desirable to do high, an understanding of the system may only allow the medium or low. Company 4 Such ranking is reasonable; the question is: what are the required levels of validation for the two highest levels? Company 5 Yes, this classification is useful. However, as low level is for internal decision, mainly medium and high level impact will be discussed with regulatory agencies. Expected level of details/validation of PBPK models should be discussed depending on medium or high level impact. Company 6 In each case, depending on the purpose, the kind of PBPK model (complexity) needed is to be defined. In that respect, this paradigm is useful. Company 7 I think it is a good starting point because in my view, the extent of the model validation should be dependent on the potential impact of the modelling. Company 8 Impact framework is useful.
2	How much background information on the disposition of the compound should be provided in the PBPK report e.g. F, Fa, mass balance data. Should authors be encouraged to develop the disposition diagram presented in Terry's presentation? (see previous PPT presentation on Topic 2).	Company 1 The report should summarise the key data in sufficient detail to support confidence in the modelling work. All key steps in model verification should be available to reviewers in the report or in linked references. An understanding of routes of elimination can be aided by the disposition diagram. However a complete understanding of all clearance routes may not always be essential; this will depend on the questions being addressed. Company 3 Any background information included should be relevant to the modelling question/application. The diagram in Terry's presentation can only be developed once radiolabelled ADME study is available. Company 2 High level background information can be given in the introduction. If such information is used in building the model itself it should be part of input parameters. Including values would generally be enough in the PBPK report, the diagram might be of help to summarize and visualize ADME properties in case of a complex profile.

Question	Question	Response
		Company 4 Without F parameter and at a lesser extend Fa, some parameters can compensate each other…and a lame parameters combination can well fit the observed data. Yes, Terry's diagrams are helpful and must guide the PBPK model validation. Company 5 Data from mass balance study are very informative but come from few subjects. *In vitro* and *in vivo* data have to be coherent. Level of required information depends on the development stage and if PBPK is used for DDI, specific population… Company 6 Obviously, as much background information as possible should be provided. Also, in that respect, the mass balance diagram (Terry's presentation) is certainly interesting to develop whenever possible. Company 7 I think it depends on the application of the model. In some cases, for example, that of ketoconazole, the disposition of the drug was not elucidated and the Company 7 model was driven by the clinical inputs. Yet, this model was applied extensively and successfully for predictions of DDIs as a perpetrator. For development of a model as a victim drug, the disposition of a drug should be described in full. However, in my view, unless metabolites are shown to be active or contribute to the inhibitory/induction potential of the drug overall, then it is not necessary to develop the disposition diagram in full. Company 8 We are in favour of sharing the background material which is used to verify the application space of the constructed PBPK model and which is considered important to generated confidence in the PBPK model.
3	What level of detail should be provided on validation of the structural model (software)?	Company 1 When commercial software is used with default structural models then validation can be made by reference to published papers. If no such validation exists then it will have to be provided by the sponsor as additional material. Company 2 The validation of the software itself is beyond the scope of a case specific report. For commercial software this step is responsibility of vendor. Only known limitations relevant to the current modelling activity should be highlighted in the report. Company 3 Reference to relevant publications and software literature/user guides should be made. Validation of relevant compound files or population files may be needed. It is important to distinguish between PBPK models that are developed by software companies in which users can select values and model options but not modify the programmed structures and models created in general purpose software (e.g., Matlab, NONMEM, acslX, Berkeley Madonna, EXCEL). For the first, companies can be asked to provide information about how they check for correct coding as versions are updated. For bespoke models, the correctness of the computer implementation also needs to be assessed, but the approaches may be somewhat different. Similar issues arise for the model structural choices. Documentation and review is particularly important for structural choices and parameter values that are highly influential for model outputs used to make decisions, so this needs to be assessed to triage efforts. Given the large, though incomplete, efforts that have gone into creating review and acceptance processes and criteria for PBPK models in environmental risk assessment, particularly for bespoke models, information from US EPA, Health Canada, nonprofits should be accessed and reviewed. Company 4 Most of the ''customers'' do not check structural models when the solfwares are bought.

Question	Question	Response
		We have no clear thought on that. Company 5 The name and version of the software has to be specified. The commercial software company is responsible for the structural model validation. For in-house model, a commented code could be provided. Company 6 Enough details should be provided to be able to check and redo the simulation. Company 7 References that have shown validation of the structural model should be cited. Company 8 Case by case. Info which is important for the specific claims of the PBPK simulations.
4	Is the level of detail on drug input parameters suggested by Zhao et al (CPT 2012, Table 2) about right? What should be added/modified?	Company 1 This paper gives one example which is about right but it does not cover all possible inputs for different types of molecule e.g. ionisable molecules, with pH dependent solubility would require additional inputs. Basically all inputs which are changed from default values should be listed. Company 2 Table structure is good. Origin and nature (measured, predicted …) of value should be clearly indicated Actual parameters will depend on software and application: - If solubility is used as input, available pH dependent and bio-relevant solubility should be detailed. - fu, inc (free fraction in in-vitro incubations) is not present in the publication and can be relevant, depending on origin of data. - If solubility, radius … are given as input (for an absorption model) I would not expect to see also Fa and Ka as inputs (they would be outputs in that type of application). - Molecular structure may be considered an input if some parameters are predicted Company 3 Yes this is about right. All compound dependent input parameters should be included in any reporting together with their source. Any 'fitting' of parameters needs to be clearly justified with explanation as to methodology for this fitting. If distributions of parameters are used, these need to be clearly specified and source information reported. While it is appropriate to focus on the drug-specific parameters, physiological parameters can highly influence results; again review and documentation may need to be different between software incorporating values selected by software developers versus bespoke models. Company 4 Roughly enough. Km values toward CYP isoforms should be added to cope with potential saturation of metabolic pathway(s). Company 5 Yes. In case of parameter optimisation, the original value could be provided and the change commented. Company 6 As mentioned in this paper, the list is not exhaustive and could be added with other specific inputs if any. Company 7 Yes. However, the table should be accompanied by text explaining how/why each of the values was selected. For example, how was the fmCYP determined from experimental data? Why was a retrograde model used to determine Clint? Was this due to under-prediction? This leads onto the next question (5).

Question	Question	Response
		Company 8 Yes
5	Model building and verification 'story': Should this be provided? And how detailed should this be?	Company 1 The report should be concise and so this "story" should be kept to the minimum necessary to provide support that the model is suitable to address the questions under consideration. Company 2 Steps followed to build model should be summarised (very briefly). Any changes to default model and optimisation undertaken should be described in more detail and justified. Company 3 The strategy and process for model building needs to be clearly described. Verification of the model should be made with any relevant in vivo data. As models get larger (e.g., >20-30 state variables), processes that may work well for documentation and review can become inefficient and cumbersome. Methods for electronic (hyperlinked) documentation have not been well developed but could be highly valuable. Consideration should be given to what would be verification (e.g. does one need to verify the software? How does one verify a specific drug/drug model? Does verification need very with the purpose of the model (e.g. high vs medium vs low)? Company 4 Yes verification should be provided, comparing simulated and observed clinical data of several clinical trials in different clinical conditions. These conditions depend on the purpose of the model. Company 5 Yes, it should be provided. The main steps should be sufficiently detailed to illustrate the level of confidence. Company 6 That's a very important point to be provided because describing the initial strategy for building the model (assumptions, initial data) and the refinement done later on based on actual data. That's increasing the confidence in the model. Company 7 Yes this should be provided. Details of the input parameter values and their selection should be provided. For example, if a range of fmCYP values are available, how was the final value selected? Based on in vitro data, a clinical study? For predictions in special populations, the development of the base model in HV should be presented first. Company 8 We find this very useful. Enough detail should be provided to verify that the model is fit for purpose.
6	Model verification: a. Should reports normally include a grid of uncertainty versus sensitivity (as per WHO IPCS publication)? And how could uncertainty be addressed? b. How best to address plausibility discussions for assumptions included in the	Company 1 This grid is useful as it brings together the uncertainty of inputs with the model sensitivity to those inputs which are important. The uncertainty of an input relies on knowledge of the assay used to generate the input as well as on experience with IVIVC for reference molecules. Plausibility can be discussed when describing the basic structural model and whenever changes are made to the default structural model. Consideration of TI should come when discussing the model sensitivity analysis as this shows the uncertainty in the model output. It could be useful to compare to historical fold-errors for similar predictions but the specific fold-error should always be discussed in the context of the questions to be addressed and the possible clinical variability. Company 2 a. Not necessarily for typical applications. Monte Carlo simulation is applied for virtual

Question	Question	Response
	model? c. How much of the report should consider the TI and the impact (low medium high as Q 1 above) of the model. d. Are targets of 0.8 to 1.25 vs. 0.5 to 2.0 helpful? Should they be decided according to the context of the use of the model?	population (and can address uncertainty wrt actual physiology of subjects). PSA on uncertain input parameters or to investigate limited predictability can address sensitivity. b. Physiological values should remain within documented limits; changes from "default" values should be justified. Input parameters are justified as above (point 4) c. These elements should not be part of report itself but of the risk assessment. Impact will derive from the objective statement (what is it intended for). TI and potential clinical relevance of predicted exposure and possible uncertainty would be part of risk assessment. d. Targets of 0.5-2.0 are generally acceptable for post-hoc verification (e.g. model used to predict human from non-clinical or new population with limited information). Tighter target may be applicable for high impact applications when extensive data is available (such as hADME, DDI studies done, different populations tested). Target limits should be considered in context of TI (clinical relevance). The context of model use (and drug TI) should always be considered. Overall, ability of model to capture trends in PK profile is as relevant as –fold error on specific parameters in evaluating performance. <u>Company 3</u> a. It is important to understand the parameters that are sensitive. This can be done using a number of plots not necessarily the ones shown in this link. b. All assumptions and rationale for these assumptions should be clearly described in any reporting. c. This again will be dependent on the application/question. d. Targets for model accuracy will be dependent on the application/question as well as compound stage and subsequent impact/decision making. Targets are also dependent upon the real experience of experimental and human variability; the 2-fold criteria was. <u>Company 4</u> a. This diagram should be useful to easily identify potential issues regarding some parameters. For some input parameters uncertainty might be difficult to characterize; For some physiological parameters the difficulty is to distinguish between uncertainty and inter-subject variability. Likely to be not so easy for some parameters. <u>Company 5</u> Uncertainty and sensitivity levels of relevant parameters should be discussed whatever the presentation format. Any assumption could be support by sensitivity analysis, or comparison to reference data/compounds. Targets of 0.8 to 1.25 vs. 0.5 to 2.0 could be helpful, but should be not limiting factors. This could be decided and discussed according the context. <u>Company 7</u> a. I don't think it is necessary to present a grid but it is important to indicate the sensitive parameters and those with uncertainty and to investigate the impact of these on the relevant parameter being predicted. b. It depends on the assumption made. c. A brief overview of the TI and the impact of the model should be provided. d. Yes but I think they should be provided on the basis of the context of the model. <u>Company 8</u> Reports should make it clear which parameters have uncertainty and what effect on outcome is. Internal strategy is always to maximally reduce uncertainty on input values. If too many input values have significant uncertainly added value of the PBPK simulations (and mechanistic basis) should be questioned. Not in favour of fixed targets. Should indeed be dependent on how accurate simulations need to be for a certain question.
7	Simulations and plots:	<u>Company 1</u> Plots of fold-error for model verification against different clinical studies can be useful

Question	Question	Response
	a. What range of plots would be best to include in the reports to show predictions and diagnostics? b. i. Should simulations normally provide geometric means and 90% PIs? Do limitations in the current models preclude the reporting of min and max? ii. Should PK profiles be presented as both log/linear and linear/linear scales? iii. Individual subject concentration data study or mean +/-SD? b. How many subjects per trial and how many trials should normally be reported (is the commonly adopted 10x10 about right)?	summaries. The type of plots used should depend on the question being addressed. Yes average and range should both be provided e.g. median and 90th – 10th percentiles. Outliers should also be considered in terms of their plausibility of occurring clinically. Both Log and linear plots are informative. For model verification mean +/- sd is OK. However consideration of outliers will require individual data. The use of trials should match the questions being addressed. Company 2 a. i. Yes, geometric mean and 90% PI is a good presentation of model output. Min and max are not as meaningful for predictions as for observed sample data. ii. PK profiles should be presented as log/linear in general to see profile over whole timeframe. Linear/linear can also be presented for better visualization around Cmax (less critical as Cmax itself is normally presented specifically in other graphs / tables) iii. Presentation of individual observed concentrations (as cloud) can allow to obtain a presentation more akin to visual predictive check in popPK and may be generally preferred. In DDI applications mean and CI are typically sufficient, individual plots may be important in special situations (e.g. poor metabolizers) b. The 10x10 design should normally cover the situation well. In some situations (e.g. very low incidence of poor metabolizers) it might be advisable to increase the size. When the model is applied prospectively (to design study) it is of interest to simulate the intended clinical trial design (n subjects x 10 trials) to evaluate how representative the proposed design is. Company 3 a. Plots to show model verification should be included i.e. any relevant clinical data that provides confidence in the model. i. geometric means and 90% PIs are sufficient. The incomplete understanding of covariance and parameter variability means min and max are not necessarily relevant. ii. this will be dependent on the scale but plots that provide confidence in model verification are key and the alternate graphing often provide clearer insights into the relationship between the simulations and data. iii. either is fine but again dependent on the question/application. b. Yes 10x10 is about right but again dependent on the question/application. Company 4 a) I: Mean and 90%CI should be provided. Min, Max predictions is out of reach of most of PBPK models. II: Yes, to illustrate different part of the profiles. III: Both Also standard observed versus predicted plots should generally be included in model evaluation processes and be reported. b) For validation, simulated trials should stick on the observed clinical trials. For the predicted data for which clinical trials were not conducted 10x10 is reasonable. The number of subjects would however also depend on changes in parameters variabilities and might be increased. Company 5 Yes, simulations should be provided as geometric means and 90% PIs. Min and max values could be not relevant because not representative of physiology conditions; P5 and P95 of simulations could be informative. Yes, PK profiles should be presented as both log/linear and linear/linear scales. Number of subject and trials can be limited by the memory management (IT and core system issues). 10x10 is manageable regarding outputs and time of simulation. Company 7 Ai) This is complicated because if a population of 100 individuals is generated, then randomly assigned to 10 x 10, then compared with an observed trial of 10 subjects, does it make sense to compare geometric means and 90% PIs of a population of 100 with corresponding data for 10 subjects from the observed clinical study?

Question	Question	Response
		ii) Yes – I usually generate both plots to check the elimination phase but generally present one or the other. iii) It should probably be dependent on the variability and the type of simulation being performed. <u>Company 8</u> -Variability on simulated parameters has historically been a significant issue at our company, but improving especially by several papers of Sugiyamas group on in vivo variability of CYP3A abundance, CYP2C19 and CYP2D6 abundance. - min max is typically off probably because crucial underlying covariates are not considered (e.g. expression of several enzymes not random but correlated to each other). - PK profiles lin and log is helpful to evaluate if shape of the curve is correct. - 10x10 is typically OK
8	Additional questions	Would appreciate a discussion on how the PBPK submission will be reviewed by the HA. Will reviewers be hands-on experienced modelers? Will there be any possibility for discussion/clarification of the model or follow up questions/requests for additional simulations? Any chance to supply model files as is done with FDA? *Attempting to provide a complete documentation of a very complex model is difficult and time-consuming. For the sponsor it is also often done under tight time constraints. Therefore to expect the written report to answer every possible question of a reviewer in advance is not realistic. Furthermore if the reviewer is not personally very experienced with the particular commercial tool used for the modelling and the most recent literature around that tool a huge number of questions are possible.*

APPENDIX 3: Detailed record of the discussion topic 1 session

Prior to the meeting, a list of perceived important model input parameters (Table 1) was sent to three software companies, and comments requested on:

- The acceptability of in silico
- What can be optimised
- Important parameters in full versus minimal models
- The use of scaling factors
- How to incorporate uncertainty.

Table 1: List of input parameters

Property	Used in software Yes/ No	Option to calculate Yes/No	Option to optimise? Yes/ No	Comments
Drug and dose form properties				
Log P				
Log D				
Acid or base				
pKa				
Solubility				
Particle size				
Dissolution data				
Drug distribution parameters				
Plasma protein binding				
Blood/Plasma partitioning				
Microsome binding				
Permeability				
Tissue Kp's				
Pharmacokinetic parameters				
Volume of distribution				
Plasma clearance				
Clearance (renal)				
Clearance (metabolic)				
Oral bioavailability				
Gut extraction				
First pass hepatic extraction				
Enzyme/ Transporter activities				
Metabolic enzyme Vmax				
Metabolic enzyme Km				
Transporter Vmax				
Transporter Km				
Enzyme Ki				
Enzyme Kinact				
Transporter Ki				
Induction Emax				
Induction EC50				

<u>Software company responses:</u>

- All the listed parameters are required.
- All three of the software companies allow in silico calculation of the parameters based on input physicochemical data (Vss, permeability etc).
- The use of in silico predictions is acceptable where the model has been validated, dependent on the application (usually early in drug development).
- Any of the parameters can be optimised based on in vivo data and should be based on a mechanistic understanding of the physiological or drug systems.
- Critical values depend on the application.

- Uncertainty is addressed with sensitivity analysis or population simulation.

The responses from the software companies were used to formulate a list of questions which were then sent to industry participants, together with the input parameter table. Industry participants were requested to rank the questions in order of importance for discussion at the meeting (Table 2).

Questions to Industry:

- Input parameters: What are the important input parameters? And for which applications. How can we take into account the uncertainty of these parameters? Are there any important or key parameters that should be available?
- Is there currently adequate consensus on the appropriate methodology for determination of key input parameters? What are the gaps?
- When are in silico calculations acceptable? Which parameters and in which setting?
- Scaling factors: When are they acceptable? Where do they come from? How can they be qualified and documented? Can they be optimised? What is an acceptable fold change?
- Definition of a sensitive parameter: Which parameters should be included in a sensitivity analysis? In what applications?
- How could sensitivity analysis be used to address lack of identifiability?
- Model improvement during the drug development: What strategy could be proposed to optimise the input parameters used as starting points? Which parameters? What is an acceptable fold change?
- How could you mitigate the adverse impact of lack of intravenous data on identifiability of drug input parameters.

Industry responses:

- All parameters are important but the order of importance will vary depending on the particular application the model is being used for.
- Uncertainty is addressed with sensitivity analysis and population analysis.
- IV data and tissue concentrations are possible important missing information.
- There is no consensus on in vitro methodology.
- In silico techniques are best conducted early in discovery. They can be used to build the SAR.
- Scaling factors are often used; varying confidence. Optimisation is acceptable but consider physiological relevance. Scaling factors need to be well qualified. Optimisation should not result in input parameter changes greater than an order of magnitude 1 respondent).
- A sensitive parameter is one that has a significant effect on prediction. This depends on the application. For sensitivity analysis, should also test uncertain values or ones that have been optimised.
- Use sensitivity analysis to identify lack of identifiabilty. Consider also the physiology. Can use further pre-clinical or clinical data to resolve.
- Parameters are optimised based on increasing knowledge. Measured values replace estimated values, followed by values optimised based on in vivo data. Optimisation should be justified physiologically and mechanistically.

- There appears to be an acceptance of lack of intravenous data. More in vitro experiments and human ADME can help. The lack of intravenous data leads to identifiability issues.

Table 2: Ranking of questions in order of importance for discussion

Question	Mean	Rank	Frequency of 1
1. Which parameters are important and how to incorporate uncertainty?	3	1	3
2. Is there a consensus of in vitro methodology?	4.5	5	0
3. When is *in silico* acceptable?	5.6	7	0
4. Scaling factors; qualification and optimisation.	3.4	2	3
5. Which parameters for a sensitivity analysis?	3.5	3	0
6. Addressing lack of identifiability	3.6	4	1
7. Optimisation of models	4.9	6	1
8. Mitigating the impact of no I.V. data	5.9	8	0

Based on the responses above, a set of questions were put together to be discussed during the meeting. Additional considerations in the selection of the questions were that there appeared to be agreement on which were the important input parameters and that uncertainty in input parameters and considerations around the lack of intravenous data would be covered in other discussion sessions. The final set of questions is shown below:

1. PBPK model improvement during drug development:

- What strategy could be proposed to optimise the input parameters for the study compound that are used as starting points?
- Is there unacceptable fold change between the initial and the optimised input parameters?
- When are scaling factors acceptable?

2. Which parameters should be included in a sensitivity analysis?

- Definition of a sensitive parameter?

3. Should there be a consensus of methodology?

- It was clear from the feedback received that there is little consensus on the appropriate methodology for determination of key input parameters. Should there be an attempt to provide a consensus of methods to be used to determine input parameters?

The discussions that took place are summarised below.

1. PBPK model improvement during drug development:

a. What strategy could be proposed to optimise the input parameters for the study compound that are used as starting points?

There was a consensus that there is a need to frame the context of the model. The importance of different parameters varies depending on the purpose of the model, and uncertainty is closely linked to the question that the model is trying to answer, so it is not possible to generalise. There is high confidence in some applications and a need to understand areas of low confidence.

There has to be a ranking of the importance of different parameters that can be measured, (e.g. protein binding) versus other input parameters, such as lipophilicity. There may be a difference in confidence between in silico derived parameters compared to in vitro parameters; the in vitro data may not be reliable. In vitro methodology can be improved to reduce uncertainty. Uncertainty around these parameters is completely independent of the model and the optimisation of the parameters has to take into account that uncertainty.

It is difficult to generate an exhaustive list of input parameters for each area of PBPK modelling (DDI, specific populations and formulation), even if it was possible to define the purpose of the model, as the categories are too broad to be able to do this. However, it may be possible to define a list of, for example, 10 important input parameters for each category.

It was questioned why the regulators were interested in how the model had evolved and how the input parameters had changed. The response was that it is of interest to see where the parameters have come from and how they affect the output of the model.

b. Is there unacceptable fold change between the initial and the optimised input parameters?

There was a discussion around what was meant by optimised input parameters. In the context of PBPK models this refers to the modification of individual parameters to make the prediction fit the observed data.

In general terms, if model predictions are systematically wrong, something is missing from the model. If something is systematically wrong in one direction, it is also possible to revise the model structure so that it is useful. If sporadic mismatches are seen, it is usually down to something specific for a particular molecule which can be identified and corrected.

There was a suggestion that agreeing an acceptable/unacceptable fold change will not be achievable until appropriate methodology has been agreed across industry.

There are other issues when looking at this – the scaling factors can be derived but it is not always clear if the in vitro data is wrong, or if it is the model that is wrong. From the literature, and as seen in previous presentations, it is clear that transporters are causing difficulties in modelling. This is due to lack of knowledge on the abundance of transporters and also there are known issues in correcting for use of a homogenate and recovery of compound from the system rather than whole cell membrane in assays, which has led to the use of scaling

factors in those assays. Thus, it is important for researchers to fully understand their assay systems rather than just applying scaling factors to make the results fit.

c. When are scaling factors acceptable?

Some scaling factors come from measurements, have been published with a global consensus, and consequently can be easily accepted e.g. MPPGL (mg of protein per gram of liver). Some others are used because there is a lack of direct extrapolation from in vitro to in vivo. Those have to be challenged with several reference compounds and well documented to be considered reliable. These empirical scaling factors are likely to be dependent on the in vitro methodology utilised and will be company- or lab-specific.

There was concern expressed over the use of scaling factors. It was suggested that the use of scaling factors is almost against the purpose of PBPK modelling. If scalers need to be used that cannot be easily justified, it suggests there is something not well understood from the current model structure. The need for scalers can be informative; however, caution should be exercised around their use, particularly if values are large.

There is no general agreement on how large a scaling factor can be and still considered acceptable. Caution was advised if the values are large (e.g. 50) and the uncertainty around the number should be considered e.g. 58 or range: 50- 70?

2. Which parameters should be included in a sensitivity analysis?

a. Definition of a sensitive parameter?

Sensitivity analyses can be global or local – for the purposes of PBPK analyses, sensitivity analyses conducted are usually local (i.e. adjustments made for parameters individually), because a significant model component, especially the system model, is considered established. Given the complexity of the model, determination of parameters for SA should be rationalised according to physiology and drug properties.

Whether a parameter is sensitive can depend on the physicochemical classification of the drug – for example the partition coefficient is more important when looking at a cationic molecule than for a neutral molecule. In other words, a set of sensitive parameters could be anticipated on the basis of the chemical structure of the compounds.

The endpoint of a sensitivity analysis should be ‘Does it modulate the dose requirements?’ This is an important question. Clearance is often the most important parameter in the modulation of dose, so it is possible to look at the parameters that drive clearance.

It was considered that a sensitivity analysis is not sufficient in itself to look at uncertainty of parameters.

Scaling factors should be explored with a sensitivity analysis.

Clinical variability should be used to inform expectations.

3. Should there be a consensus of methodology?

It was clear from the feedback received that there is little consensus on the appropriate methodology for determination of key input parameters.

a. **Should there be an attempt to provide a consensus of methods to be used to determine input parameters?**

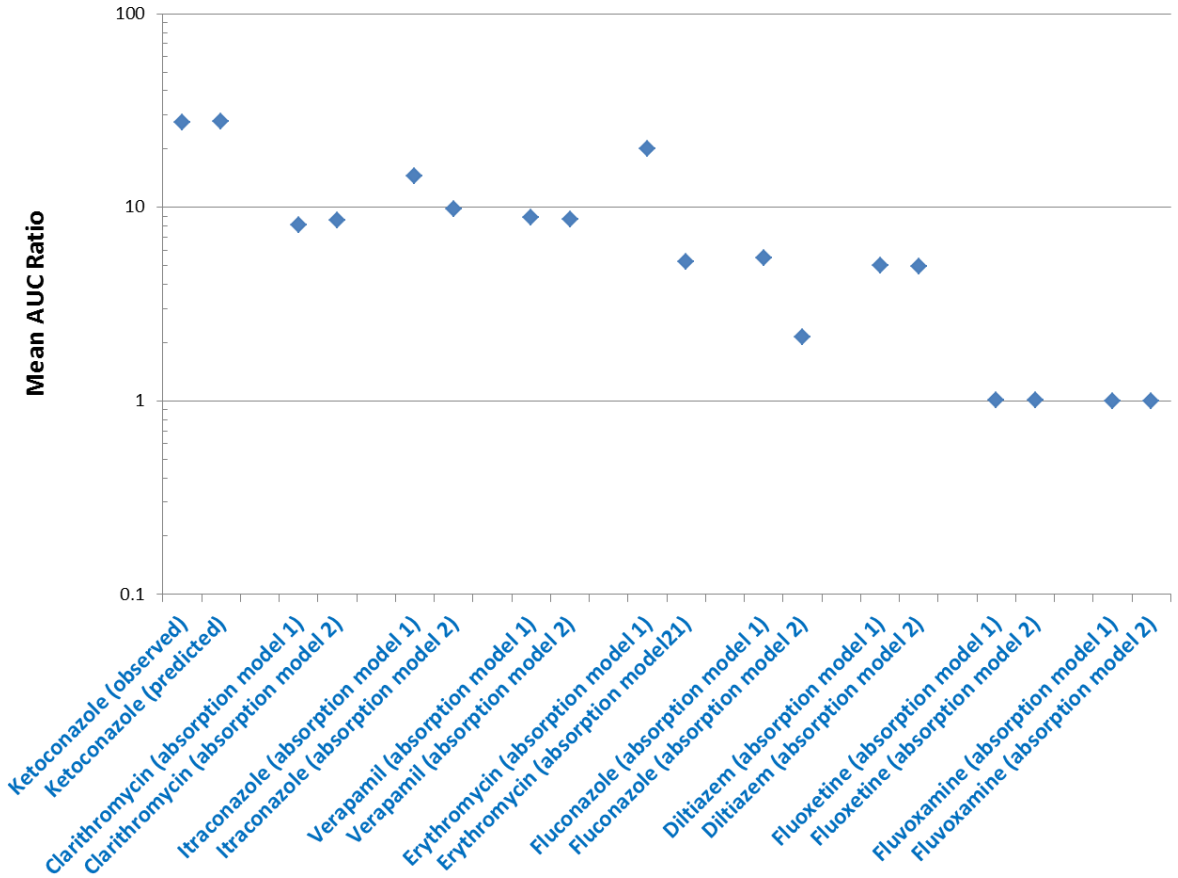
Whilst considered highly desirable, the ideal of a standard in vitro methodology across the industry was not thought to be a realistic aim. Rather, a full understanding and description of methodology with adoption of common reference standards to be utilised across companies should be encouraged.

APPENDIX 4: Detailed record of the discussion topic 2 session

Prior to the meeting, delegates were provided with 4 examples of PBPK models of high regulatory impact, based on recent submissions to European regulatory agencies, and asked to provide feedback in response to a set of questions. Some of these questions were explored further during the meeting. Individual responses are listed in Appendix 2; a summary of the pre-meeting feedback and discussions during the meeting are presented below.

Objective of session: To discuss the verification of PBPK models and to explore and define best practice around the use of ADME (in vitro and in vivo) and other in vivo data in the verification of drug-specific input parameters for an NCE. The question was framed as supporting a high impact regulatory decision.

Example 1:



Example 1 pre-meeting feedback:

1) **Are these data presented adequately? If not, what else would you expect to be presented?**

The consensus was that the data were not adequately presented. Delegates would like to see the following:

For verification

- C(t): simulated profiles with observed data superimposed for both administrations (with and without ketoconazole)
- C(t) variability: individual observed data with geomean/median with 10/90 percentiles for predictions or VPC
- PK parameter values (i.e. in addition to ratios), including Cmax
- PK parameter variability: predicted and observed CV% or 95% confidence intervals for Cmax and AUC and parameter ratios

For simulation

- Information on dose and dose regimen of inhibitors
- Validation data for each of the inhibitor models
- Predicted variability, including ratios (extreme values important for DDI)
- Sensitivity analysis to understand potential impact of assumptions on modelled output; Explanation of different absorption models or choose one – the best one.
- On graph, include different decision making areas (e.g. ratio < 2, 2<ratio<5). Especially area associated with adverse events.

2) Based on the observed and predicted data, would you be confident in the predictions of the extent of interaction with moderate and weak inhibitors of CYP3A4?

No, there is too much information missing.

3) Would you be comfortable to support the team's position that the clinical pharmacology package related to DDI is complete (i.e. using PBPK for extrapolation)?

No, there is too much information missing

4) If not, what additional studies and/or analyses would you expect to give you the necessary confidence?

Confidence could be increased by additional analyses including:

- Time and dose dependency of compound pharmacokinetics.
- Validation using other studies, e.g. phase II/phase III studies.
- PBPK model assumptions.
- Sensitivity analysis around key parameters.
- Hypothesis testing around contribution of intestinal and liver metabolism: shape of C(t) before and after Cmax captured?
- Differences in Cmax might indicate transporter involvement.
- Verification of other inhibitors (using substrates with PK properties close to studied compound); need to understand reason for inconsistent results for strong and moderate/weak inhibitors.
- Overall safety profile and efficacy window to contextualize the DDI findings.

Confidence could be increased by additional data including:

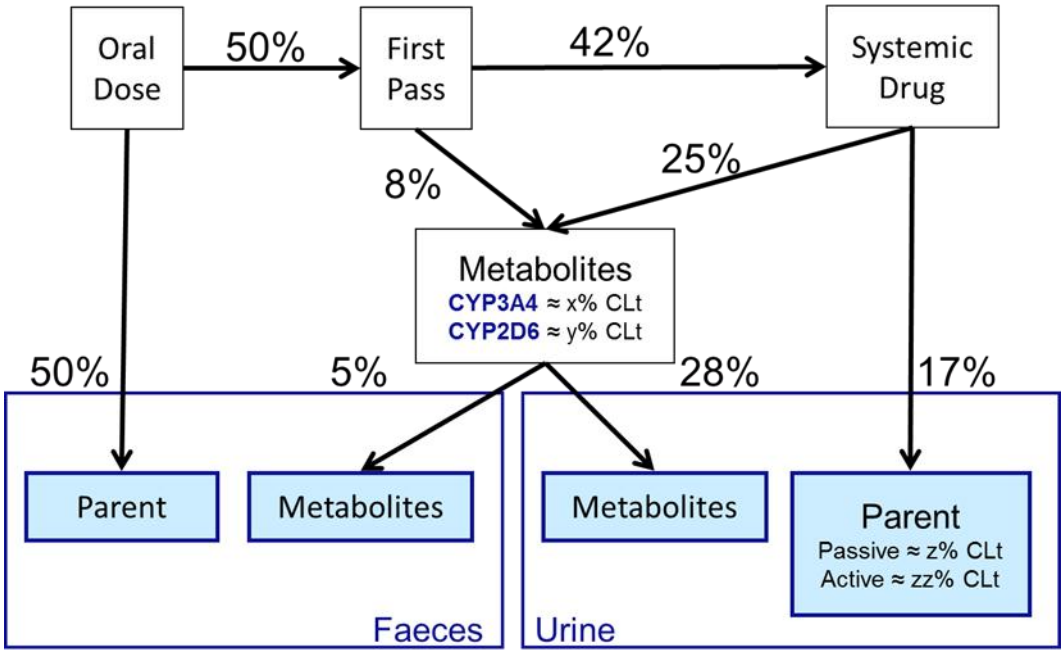
- Contributions of intestinal and liver metabolism (both to be investigated); clinical data allowing verification of Fg, Fh and fm CYP3A. This requires clinical data to define routes of elimination and disposition PK (IV study); data to give confidence in simulated fa.
- Full in vitro package; in vitro enzymes involved in metabolism and in vivo metabolite profiles.
- Study with a moderate inhibitor and/or weak inhibitor; common co-meds that inhibit CYP3A; confidence high if can predict ketoconazole interaction from in vitro intrinsic clearance.
- Data to exclude other mechanisms of ketoconazole interaction (CYP2J2, esterases); data to support that no other enzymes are involved.
- Evidence that transporters are not important.

5) **Would the addition of predicted and observed interaction with a strong inducer increase your confidence in the predictions for co-administration of moderate and weak inhibitors of CYP3A?**

The majority view was that it would add confidence around fmCYP3A. The minority view was that this would give no increase in confidence. It was also highlighted that independent of PBPK, it is possible to predict the impact of moderate and potent inducers if the contribution of CYP3A4 to oral clearance is known.[11]

Example 2:

The objective of this PBPK exercise was to identify subpopulations at risk of DDIs for this new drug. The quantitative mass balance diagram below was included to support the discussion of the biological plausibility of the PBPK model.



[11] Ohno et al 2007. Clin Pharmacokinet. 2007;46(8):681-96.

Example 2 pre-meeting feedback:

1) **What in vitro and in vivo studies would you expect to find listed in the Summary of Clinical Pharmacology to support this diagram and give you confidence that the risk assessment is unreliable?**
2) **What specific studies would give you confidence in the partitioning of hepatic clearance across different pathways?**

Studies should answer the following questions:

- What are the clearance pathways?
- What are their quantitative contributions?
- What is the extent of absorption of the drug and is parent drug in faeces a result of lack of absorption or biliary excretion (fa)?
- What is the extent of first pass metabolism and what are the contributions of intestinal and hepatic first-pass?
- What is the rate-limiting step for hepatic drug clearance (metabolism or uptake)?

In vitro studies

- Metabolism studies; phenotyping of involved CYPs; in vitro studies with HLM and specific inhibitors
- Transporter studies (gut efflux, renal and hepatic transporters)
- Solubility and permeability
- Metabolite ID
- Plasma protein binding
- Blood to plasma ratio

In vivo studies

- Mass balance study PO
- DDI with specific inhibitors (e.g. 2D6, 3A4)
- CYP2D6 PM vs CYP2D6 EM
- IV data
- Preclinical ADME with IV and biliary data
- Mass balance study IV.

Example 3:

Your drug is administered orally and is found to inhibit CYP3A4 in vitro. In your company IC_{50} is routinely used for inhibition. No TDI data are available. In the first step of evaluation, I/Ki suggests the possibility of an in vivo interaction. A PBPK simulation is then performed and suggests no in vivo interaction.

Example 3 pre-meeting feedback:

1) **What sensitivity analysis is crucial for this simulation?**

Parameters:

- Ki! (and should be determined not via IC_{50}/2 or show that you do not have a TDI).
- fu_p, fu_{mic}, fu_{gut} (depending on GIT model utilised), permeability.

Simulations for sensitivity evaluation:

- Liver /Intrahepatic concentration ("confidence that liver drug concentration exposed to liver CYP3A4 is correctly captured").
- Intraenterocyte concentration.

2) **Based on rat QWBA data it is suggested that there is higher liver concentration compared to blood. Will that impact the analysis you would expect to see, and if so, how?**

Approximately half of the responders thought it could or would add confidence:

- Compare the predicted liver:blood partition ratio (Kp) to what was observed from rat QWBA
- Do sensitivity analysis on hepatocyte accumulation

Approximately half of the responders thought it would not add confidence:

- Done in rats, not humans; QWBA uses radioactivity (parent+ metabolite)
- Not useful. If human in vitro uptake liver transporter data showing the drug as a good substrate that should be more of a consideration.
- High tissue concentration does not necessarily represent high unbound concentration. Liver tissue binding can be determined in vitro.

Example 4:

The transporter OATP1B1 is involved in the hepatic uptake of your new drug. Metabolism via CYP3A is a large part of the elimination of the drug based on in vitro and in vivo data. The pharmacokinetics shows nonlinearity within the therapeutic range (this could be assumed to be both related to OATP1B1 and CYP3A).

Example 4 pre-meeting feedback:

1) **What are you comfortable to predict using PBPK for this drug?**

All those who responded were comfortable to predict using PBPK for this drug:

- Mechanistically explain the impact of various intrinsic/extrinsic factors between the studied populations but not comfortable using it to extrapolate to a new population.
- Use for hypothesis generation and learning

Additional data required if using for high regulatory impact application (waive study) would include:

- Needs understanding of the IVIVC of OATP.
- Vmax and Km for both the enzyme and the transporter (several).
- Good to have two DDI studies done to confirm modelling (OATP and CYP3A inhibitors); or OATP1B polymorphism.
- + confidence that non-linear PK is mechanistically built in correctly in the model
- Thorough model validation is important for a complex interaction model.
- Concern regarding translation of in vitro transporter kinetic data to the in vivo situation (from several).

Based on the answers provided above, the following questions were discussed in the meeting in order to explore some of the feedback in more detail.

1. **According to the feedback received, the following points were identified as important to support a quantitative mass balance diagram from Example 2: (1) what are the clearance pathways? (2) what are their quantitative contributions? (3) what is the extent of absorption of the drug and is parent drug in faeces a result of lack of absorption or biliary excretion (fa)? (4) what is the extent of first pass metabolism and what are the contributions of intestinal and hepatic first pass? (5) what is the rate limiting step for hepatic drug clearance (metabolism or uptake)?**

   Do you agree that these are the necessary questions to answer?

Yes, but there was also consensus that these are questions that should not just be answered when looking at PBPK, but should be answered as part of standard drug development. It was also acknowledged that a less detailed PBPK model would be adequate for evaluation of a potential perpetrator (enzyme inhibition).

2. **The following in vitro studies were identified as part of a clinical pharmacology package supporting the mass balance diagram in Example 2: (1) metabolism studies, phenotyping of involved CYPs, in vitro studies with HLM and specific inhibitors, (2) transporter studies (gut efflux, renal transporters), (3) solubility and permeability, (4) metabolite ID, (5) plasma protein binding, (6) blood to plasma ratio. The following in vivo studies were identified as part of a clinical pharmacology package supporting the mass balance diagram: (1) mass balance study PO, (2) DDI with specific inhibitors (e.g. 2D6, 3A4), (3) CYP 2D6 PM vs CYP2D6 EM, (4) IV data, (5) preclinical ADME with IV and biliary data, (6) mass balance study IV.**

   Under what specific circumstances could a quantitative mass balance diagram be constructed with confidence, even though IV data are unavailable?

In general attendees agreed that IV data can be important (depending on the pathways being modelled) and the value of this should not be underestimated. However, it was recognised that it is easier to say it should be obtained than to obtain it in practice, due to competing priorities and budgets within companies. It is often difficult to justify to clinical teams that an absolute bioavailability study is useful. If a regulatory authority or regulatory

guidance states that IV studies should be done, then clinical teams will comply. This is not a question of patient safety as there are no safety implications in doing IV studies, which use very low doses (e.g. microtracer IV dose administered in addition to a pharmacological oral dose); however time and cost may be factors. The benefit that can be gained from collecting these data is a price that would be recovered from not having to conduct a DDI study at a later date. The real question should be when it should be done during the programme. It is important to build the arguments for performing this type of study into the clinical plans at an early stage.

A key recommendation from this meeting is therefore to develop a statement around the "general expectation of IV data generated", supported by a clear rationale.

There was a discussion about whether preclinical IV data might be useful where clinical data cannot be obtained. There was no single answer to this question as it very much depends on the drug types and the similarity between animals and humans. There are some IV profiles that look the same across species; however there are others where transporters are different and then the profile will be different. If pre-clinical IV data is used, its relevance to humans has to be very clearly justified.

When regulators assess submissions that do not contain IV data, they assess the implications on the label of not having IV data, taking into account the totality of the data.

There are certain clinical scenarios in which IV data might not necessarily be required. It is very much dependent on the pathways involved.

3. **The in vitro/in vivo extrapolation for inhibition is different from that of induction (example 1). When a compound is a perpetrator of induction of PXR, the DDI GL in Europe suggests the use of the RIS (relative induction score) method using many calibrators.**

   Are there data to give confidence in the use of a single calibrator for PBPK simulation of induction, particularly where the simulation is to be used to support waiver of an in vivo induction study?

For simple CYP3A4 induction, this can be done with some confidence. The EMA DDI guideline states that if the compound has a large CYP3A4 component, there is no need to conduct a rifampicin study. When it comes to moderate inducers, studies can add confidence and reduce uncertainty about the overall evaluation of the drug. There are opportunities to use what is understood about a molecule to define what would be an appropriate approach based on physicochemical relationships.

Often in rifampicin studies there is not a full set of clinical data showing the concentration profile of both rifampicin and the test drug, so it is not possible to link them directly. It is generally assumed these markers have a 1:1 relationship with CYP3A4; however this is not necessarily the case and they are not always a direct measure of Cl_{int}.

4. **What additional analysis is needed under the construction of a PBPK model and during the analysis of for example a drug-drug interaction (example 3)? How should the range of sensitivity analysis be defined?**

It depends on physiochemical properties and/or experimental systems. For example, there is a tendency for systematic overprediction of TDI using microsomes compared to hepatocytes, therefore this knowledge can be used to guide the range of sensitivity analysis.

In the example, data are missing that link in vitro Ki and in vivo DDI results. Looking at KI, K_{inact} and K_{deg} all together could inform the range for sensitivity analysis.

Consideration also needs to be given as to whether the drug is a substrate for an inhibited enzyme; if so, this requires optimisation based on in vivo data.

Experimental approaches may be more informative in some cases (e.g. looking at free concentrations in liver/enterocyte).

APPENDIX 5: Detailed record of the discussion topic 3 session

The session began with a series of presentations from 3 software companies. Summary slides were then presented to frame the background for the discussion. All 3 companies generally appeared to take similar approaches to validation of their software.

Some thoughts from the organising committee comprising representatives from industry, academia and the regulatory sector were also presented:

- PBPK modelling in regulatory submissions is in its infancy.
- Confidence in the models needs to improve.
- Data sets change e.g. change from the use of ketoconazole to the use of itraconazole in industry.
- Proprietary data is used extensively by companies.
- Data sets need to evolve as the software evolves.
- A central repository of libraries with well characterised examples that can be used to qualify new models would be ideal.
- A qualification document (reference) that establishes the validity of the systems in which we build our drug models (version update) is needed.
- A document explaining the sources of the parameters and the description of the tests and the results obtained to qualify them (version update) is also needed.

Output from discussion topic 3 (with software company representatives)

Where are we going in terms of system qualifications?

The term “system qualification” as opposed to “system validation” was questioned and it was suggested that the correct terminology needs to be decided among the community.

There was a discussion on the added value in PBPK models being mechanistic vs. empirical. It was agreed that more complex models based on physiological structure can identify additional covariates, giving a greater ability to understand the drugs and enable extrapolation to different scenarios e.g. inter-species, inter-populations. For example a typical basic oncology drug was modelled and the researchers saw variability but were unsure as to the reason behind this phenomenon. A more complex model that included additional factors, including what was eaten, found that precipitation of the drug in the stomach was causing the variability observed.

There was an opinion expressed that there is no excuse not to include verification in PBPK modelling. Uncertainty in parameters should be propagated through to the final output. However, it was argued that the correlation between parameters increases the difficulty of doing this. Model qualification should not only focus on single parameters (AUC, CL, Volume) but should pay attention to the concentration profile; not only plasma or blood but also tissues.

The importance of input parameters was again highlighted. Does the model offer an improvement over the assumption e.g. that the parameter is equal for all compounds in the data set?

From a regulatory perspective, it comes down to clinical context. The focus for regulators is not about the models and systems per se, but more the clinical impact of the outcome and the consequences for the patients. Therefore it is important to understand the models being used.

Where are the gaps?

There is a need for agreement of terminology; 'system qualification'?

There can often be the assumption that each parameter has an independent distribution; however, in physiology parameters are often highly correlated. When performing the PBPK modelling, the researcher is unlikely to know fully how all the different parameters interact and that is an important gap in knowledge. There is also a lack of qualified libraries for all applications. Previous real data on which to base PBPK models contained within these libraries would be hugely informative.

This is a rapidly evolving area and there is a lot to consider; further discussion is needed before concrete recommendations can be made.

What are the potential approaches to fill these gaps?

Although it may not be possible to fully account for correlation of all covariates in the model, it should be possible to model a 'best' (or worst) case.

Prior and emerging knowledge can be used to modify and improve the models on an on-going basis. The greatest progress is currently being made in libraries qualification for the patient populations. As more data are being published these are being refined and added to.

Follow-up discussions to define terminology are needed to address specifics aspects, for example the incorporation of uncertainty in system parameters.

APPENDIX 6: Detailed record of the discussion topic 4 session

A summary of the pre-meeting feedback and discussion points is provided below.

Pre-meeting feedback

Question 1: How should the purpose of the modelling effort best be framed?

- Generally many think some classification is useful.
- Aim and purpose of modelling should be clearly described together with impact on decision making.
- Internal decision making may still be relatively high impact to the program.
- The question is: what are the required levels of validation for the two highest levels of regulatory impact?
- The extent of the model validation should be dependent on the potential impact of the modelling.

Question 2: How much background information on the disposition of the compound should be provided in the PBPK report e.g. F, Fa, mass balance data. Should authors be encouraged to develop the disposition diagram presented in Session 2 presentation?

- Background information is of limited value without integration. There is general agreement that this is a good idea; the question here is how much information should be included.
- Need for background information on the disposition of the compound depends on the purpose and aim of the modelling study.
- An understanding of routes of elimination can be aided by the disposition diagram. However a complete understanding of all clearance routes may not always be essential. This will depend on the questions being addressed.
- High level background information can be given in the introduction. If such information is used in building the model itself it should be part of input parameters.
- The information needed also depends on when, NCE/NDA or earlier.

Question 3: What level of detail should be provided on validation of the structural model (software)?

- The validation of the software itself is beyond the scope of a case specific report. For commercial software this step is responsibility of vendor. Only known limitations relevant to the current modelling activity should be highlighted in the report
- Reference to relevant publications and software literature/user guides should be made. Validation of relevant compound files or population files may be needed.
- Enough details should be provided to be able to check and redo the simulation.

Question 4: Is the level of detail on drug input parameters suggested by Zhao et al (CPT 2012, Table 2) about right? What should be added/modified?

- The suggested level of detail is acceptable.
- List of parameters depends of purpose of modelling and software

- Origin and nature (measured, predicted …) of value should be clearly indicated, source
- The table should be accompanied by text explaining how/why each of the values was selected
- Any 'fitting/optimisation' of parameters needs to be clearly justified with explanation as to methodology for this fitting.
- If distributions of parameters are used, these need to be clearly specified and source information reported.
- Added: fu_{inc}, molecular structure, available pH dependent and bio-relevant solubility
- Range should be clearly defined.

Question 5: Model building and verification 'story': Should this be provided? And how detailed should this be?

Provide model building and verification story?

- With enough detail to reproduce the process.
- Strategy and process needs to be clearly described.
- Should be kept to minimum necessary to support that the model is suitable to address the questions under consideration
- Summarise (very briefly) steps followed to build model. Any changes to default model and optimisation described in more detail and justified.

Vary with purpose?

- As models get larger processes that may work well for documentation and review can become inefficient and cumbersome
- That's a very important point, assumptions, initial data and the refinement done later on based on actual data. That's increasing the confidence in the model.
- Consideration should be given to what would be verification (e.g. does one need to verify the software? How does one verify a specific drug/drug model?

Question 6: Model verification:

a. Should reports normally include a grid of uncertainty versus sensitivity (as per WHO IPCS publication)? And how could uncertainty be addressed?

- To be further discussed in light of the complexity of PBPK models in drug development
- Useful
- Not necessarily for typical applications. PSA on uncertain input parameters or to investigate limited predictability can address sensitivity
- It is important to understand the parameters that are sensitive. This can be done using a number of plots not necessarily the ones shown in this link.
- For some input parameters uncertainty might be difficult to characterize
- Uncertainty and sensitivity levels of relevant parameters should be discussed whatever the presentation format and the impact.
- If too many input values have significant uncertainly added value of the PBPK simulations (and mechanistic basis) should be questioned.

b. How best to address plausibility discussions for assumptions included in the model?

- Physiological values should remain within documented limits; changes from “default” values should be justified.
- Input parameters are justified.
- Plausibility of assumptions and rationale to be discussed in the modelling report.
- Any assumption could be support by sensitivity analysis, or comparison to reference data/compounds.

c. How much of the report should consider the Therapeutic index and the impact (low medium high as Q 1 above) of the model.

- These elements should not be part of report but of the risk assessment/conclusions.
- Target indication and impact of conclusions set the frame for modelling effort.
- A brief overview of the TI and the impact of the model should be provided.

d. Are targets of 0.8 to 1.25 vs. 0.5 to 2.0 helpful? Should they be decided according to the context of the use of the model?

- Targets of 0.5-2.0 are generally acceptable for post-hoc verification
- Tighter target may be applicable for high impact applications when extensive data is available
- Target limits should be considered in context of TI (clinical relevance) and real experience of experimental and human variability
- Ability of model to capture trends in PK profile is as relevant as –fold error on specific parameters in evaluating performance.
- Not in favour of fixed targets. Should indeed be dependent on how accurate simulations need to be for a certain question.

Question 7: Simulations and plots:

a) What range of plots would be best to include in the reports to show predictions and diagnostics?

- Plots can convey information efficiently: use whenever applicable, e.g. for concentration-time-profiles, sensitivity analyses
- Plots with fold error to show model verification

i) Should simulations normally provide geometric means and 90% PIs? Do limitations in the current models preclude the reporting of min and max?

- Mean and range should both be provided e.g. median and 90th – 10th percentiles. Outliers to be considered and discussed.
- Min, Max predictions are out of reach of most of PBPK models.

ii) Should PK profiles be presented as both log/linear and linear/linear scales?

- PK profiles shown on both linear and log-linear are helpful to evaluate if the shape of the curve is correct.

iii) Individual subject concentration data study or mean +/-SD?

- Presentation of individual observed concentrations (as cloud) → presentation more akin to visual predictive check in popPK and may be generally preferred. In DDI applications mean and CI are typically sufficient, individual plots may be important in special situations (e.g. poor metabolizers)
- For model verification mean +/- SD is acceptable. However consideration of outliers will require individual data.
- Also standard observed versus predicted plots should generally be included in model evaluation processes and be reported.

b) How many subjects per trial and how many trials should normally be reported (is the commonly adopted 10x10 about right)?

- For predicted data 10X10 is about right
- For validation stick to observed number

Discussion key points

Some of the above questions were also discussed during the session. A record of the discussions is provided below:

Question 5: Model building and verification 'story': Should this be provided? And how detailed should this be?

There are two opposing arguments here from industry: 1) the final model used is more important that the development history, so it is unnecessary to provide that information to the regulators; or 2) in order to provide confidence in the final model it is important to provide the details of the development history.

From a regulatory perspective, it is sometimes not particularly clear as to why a PBPK model has been used, so the objectives need to be clear

It might be easier to generate a clearer story if PBPK plans were produced before work was conducted. Given that PBPK modelling is an "up-and-coming" speciality in industry, it can be difficult to get the budget to allow it to fulfil its potential. Producing a PBPK plan, or including PBPK thinking and rationale into the clinical plan may help secure the budget and plan for future work.

On the other hand, PBPK is more of an approach to drug development rather than a simple tool. It includes the entirety of the knowledge of drugs, disease, physiology, etc. PBPK models are built over time with all this information feeding into them on an on-going basis. They aren't built for particular purposes as with other types of modelling (e.g. pop PK models) and it is therefore more difficult to write plans.

PBPK models can be central to drug development. Indeed PBPK can help improve understanding; however when the regulators see a PBPK report, it needs to be clear why it has been used and its purpose and impact within the context of the regulatory submission..

From the perspective of a software company, when PBPK work is outsourced to a software company, a plan is put in place up-front so that the objectives and rationale are very clear. This is not always the case in-house when a compound may have years of data behind it.

Question 6: Model verification:

a. Should reports normally include a grid of uncertainty versus sensitivity (as per WHO IPCS publication)? And how could uncertainty be addressed?

b. How best to address plausibility discussions for assumptions included in the model?

c. How much of the report should consider the Therapeutic index and the impact (low medium high as Q 1 above) of the model.

The reports should be written in context and should address the main question and clinical context of whether the report will result in a change in dose recommendation. Therefore the therapeutic index and impact should be included.

Regulatory authorities often receive PBPK reports that include predictions. Two questions need to be considered: 1) is the interpretation correct, and 2) what are the implications. Companies should be interpreting their PBPK data, integrating it with the rest of the clinical data and determining its implications. They should also ascertain what to include in a submission and how this should be done. This should be clearly explained to the regulators.

Indeed, when submitting PBPK reports, a clear purpose should be stated up-front. While it is accepted that PBPK modelling can have a range of uses for internal decision-making and building a story on the compound, when PBPK reports are submitted to regulatory authorities then there has to be a clear purpose for doing so and the reports should be written to support that purpose.

d. Are targets of 0.8 to 1.25 vs. 0.5 to 2.0 helpful? Should they be decided according to the context of the use of the model?

It was agreed that the clinical context is much more important that the targets indicated. Indeed, the '0.8 to 1.25' target has come from bioequivalence limits, which are not applicable for PBPK so can be discounted.

One participant indicated that if the AUC and C_{max} ratio was not below 1.25, they would consider optimising the model.

Question 7: Simulations and plots:

a) What range of plots would be best to include in the reports to show predictions and diagnostics?

i) Should simulations normally provide geometric means and 90% PIs? Do limitations in the current models preclude the reporting of min and max?

ii) Should PK profiles be presented as both log/linear and linear/linear scales?

This is not a major issue from a regulatory perspective and there was no strong opinion on which should be presented.

iii) Individual subject concentration data study or mean +/-SD?

b) How many subjects per trial and how many trials should normally be reported (is the commonly adopted 10x10 about right)?

Historically, 20 trials with 10 participants in each trial were used. The 10 virtual participants reflected the typical size of clinical study but the 20 replication of random selection of trials was chosen such that if none of the predictions from the 20 trials matched what was observed in clinical study, this indicated that the model needed further optimisation (i.e. the chance of the model being consistent with observations being <5% [1 in 20]). This has been decreased to 10 trials with 10 participants in each trial (i.e. a total of 100 participants) to save simulation time. This is still useful in that it shows the full distribution of the data although to assess the consistency with limited study data, running more virtual trials (20 or higher) might be useful.