Event	Faculty
Breakout Session A: Best practices for solubility as input to PBBM	**Speaker**: Deanna Mudie, Lonza **Moderator 1:** Evangelos Kotzagiorgis, EMA **Moderator 2:** Claire Mackie, Janssen **Scribe 1:** Tessa Carducci, Merck **Scribe 2:** Mario Cano Vega, Amgen

Q1. Aqueous and Biorelevant solubility – what are we measuring and why?

a. Bulk and surface solubility
   i. How to model surface solubility for free forms, salt forms, and impacts of ionizable excipients on bulk and surface pH. When does it matter and what if it is important to accurately capture bulk and surface pH as different values?
   ii. What are the deviations from theory and how best to handle these
   iii. Handling in the different softwares (current understanding: SimCyp simulator models different bulk and surface pH values, GastroPlus uses a single pH value within each compartment)
   iv. How to verify the assumptions (clarity for regulators)

b. Approaches for biorelevant solubility in the fed state
   i. Which media to choose (FeSSIF V1, V2?) to be able to compare to the in vivo situation (presence of e.g., bile salts and concentration, fats in the stomach, buffer pH)
   ii. How to simulate bile salt solubilization? Does one SR factor work for all bile conc.?
   iii. When to measure solubility in human aspirates? How to enter solubility measurements in human aspirate since composition is much more complex?
   iv. For weak bases – added value of measuring as wide as pH 8-9 and if so which media?
   v. Handling in the different softwares (e.g., default physiology vs can we adapt)
   vi. How to verify the assumptions (transparency for regulators)

Q2. Amorphous solubility – what should we be measuring?

a. What solubility value should be used for release from an e.g., amorphous solid dispersion containing a polymer? This value can impact both dissolution rate and extent of dissolution in each compartment.
   i. In some cases, the polymer type can impact the apparent solubility of the drug
   ii. In some cases, the release rate of drug from the ASD is not proportional to drug solubility, but instead to polymer solubility or an intermediate value between the two
   iii. Is the value kinetic or thermodynamic?
   iv. How to handle in the different softwares

Q3. Parameter sensitivity analysis (PSA) - how wide should we go?

a. Should this include, API properties, DP properties, bile acids, pH, intestinal factors, other factors?
b. How to visualize “space” explored in the PSA including any impact (transparency for regulators)?
c. Should we have an approach per BCS and/or formulation platform (e.g., IR conventional, IR ASD)

Q4. If time permits –

a. Similar as for ASDs, solubility in lipids and how to handle in the softwares
b. Alternative techniques for measuring API solubilities for APIs which are unstable as a function of the GI pH range

Q5. Desired outcome - a decision tree/framework - likely we would need to factor in formulation platform to this i.e., conventional or enabling (ASD) and have 2 prongs if you will - Decision tree A and Decision tree B

Breakout Session B: Dissolution Part 1: Best practices for data generation as input to PBBM	**Speaker**: Raimar Loebenberg, Univ of Alberta **Moderator 1:** Paul Seo, FDA **Moderator 2**: Nikoletta Fotaki, Univ of Bath **Scribe 1:** Parnali Chatterjee, FDA **Scribe 2:** Ivy Song, Takeda

Quickly (re)present definitions of methods

Q1. What are the main physicochemical parameters you consider for your dissolution development?

- BCS class
- Dose number
- Dissolution number
- Level of discrimination
- Other?

Q2. Selection of variants for clinical study: What difference is expected?

- Depending on the drug substance and formulation, to demonstrate bio-relevancy and discriminating ability of the dissolution method at what range (+/-10-20% or higher of Target formulation) are critical bioavailability attributes (critical material attributes, critical formulation variables, and critical process parameters) evaluated? What criteria, if any, are used to select variant formulations for evaluation in pilot BA studies?

Q3. How many different experimental dissolution data should be generated for single batch?

Q4. What are the pitfalls of dissolution (e.g., degradation, mixture of polymorphs, precipitation) etc. to be careful about and how to deal with it?

How do you separate artifacts of the dissolution test and its significance (or nonsignificance) on in vivo response (e.g., coning is often a dissolution issue, but is minimally a concern in vivo. How do we determine when this is significant enough for further study?)

Q5. How to make use of biorelevant dissolution (e.g., multi-compartmental).

Suggested deliverables: Decision tree on how to appropriately select a dissolution method and what are the pitfalls to look at when interpreting data

Breakout Session C: Dissolution Part 2: Best practices for modeling dissolution as input to PBBM	**Speaker**: Xavier Pepin, Simulations Plus **Moderator 1:** Luiza Borges, ANVISA **Moderator 2:** Cordula Stillhart, Roche **Scribe 1:** Grace Chen, Takeda **Scribe 2:** Megerle Scherholz, BMS

Q1. What is the appropriate dissolution model for an IR formulation?

a. Overview of dissolution models with rationale for choice for each model
b. Present a draft decision tree for dissolution model selection as a starting point for the discussion

Deliverable: Decision tree on how to choose a model for IR product dissolution

Q2. What are the input parameters required to mechanistically evaluate in vitro dissolution data?

a. List of parameters to consider/collect for in vitro model development, such as concentration of surfactant, size of micelles, solubility at the drug surface (micro-environmental pH), impact of excipient.

b. List of properties or processes to be mindful about: Degradation in solution, precipitation, form change, assay, solubility limitation, interaction with excipients, wettability, interaction with another drug or component, in vitro artifacts (e.g., sedimentation)

Deliverable: Checklist of criteria which have to be addressed in order to ensure robust in vitro model development

Q3. What are the criteria and acceptable thresholds for in vitro dissolution model verification?

a. List of possible criteria for discussion (e.g., AFE, AAFE, PE%; Should we compare different models and pick the right one from these parameters or should we go all the way to integration in the PBBM and then choose?)

Deliverable: Definition of an acceptable level of in vitro dissolution model verification

Q4. What is an appropriate quality and quantity of data to be generated to allow dissolution model validation?

a. List of options: # of batches, # of dissolution conditions, # different pH conditions

Deliverable: Provide clear guidance on the dataset required for model validation.

Q5. What is the appropriate approach for in vitro dissolution modelling of modified release formulations? What are challenges and gaps?

Breakout Session D: Best practices for integration of precipitation in PBBM	**Speaker**: Christian Wagner, Merck group **Moderator 1:** Poonam Delvadia, FDA **Moderator 2:** Mark McAlister, Pfizer **Scribe 1:** André Dallman, Bayer **Scribe 2:** Elizabeth Gray, FDA

Q1. Best practices for modelling precipitation under physiologically relevant luminal conditions – First order fixed rate constant/mechanistic nucleation and growth predictions in dynamic pH/fluid volumes?

Q2. How do we model precipitation from supersaturating delivery systems such as amorphous solid dispersions – what are the options to account for complex speciation including liquid-liquid phase separated nanodroplets?

Q3. Options/best practice for characterizing (or predicting) precipitated material attributes (form, particle size, solubility) for accurate input to PBPK models?

Q4. Can we identify the class of compounds for which the need to integrate a permeation-like process in the precipitation assay is essential for accurate estimation of precipitation and what are the suggested experimental options for this?

Q5. Which limitations of commonly used in vitro precipitation assays based on transfer methodology can be addressed by improved experimental design?

Breakout Session E: Best practices for integration of permeability in PBBM	**Speaker**: Hans Lennernäs, Uppsala University **Moderator 1:** Christer Tannergren, AstraZeneca **Moderator 2:** Rodrigo Christofoletti, Univ of Florida **Scribe 1:** Xiaojun Ren, Novartis **Scribe 2:** Eleftheria Tsakalozou, FDA

Q1. What are the available methods to estimate jejunal Peff and what is the rank order between the methods wrt confidence in the Peff estimation?

Q2. Confidence in Peff estimation – Low vs High permeability compounds?

- How to use in vitro permeability data generated in biorelevant media as input?

Q3. Papp-Peff correlation vs fitting Peff to observed data – When to do what?

Q4. When can permeability input into PBBM be based on passive permeability alone and when is there a need to account for uptake/efflux transporter mediated transport?

- What is the current best practice to account for uptake/efflux transporter mediated transport?

Q5. Regional permeability?

- What is the confidence in using the estimated jejunal Peff to define the Peff in the other compartments?
- How can we estimate a colon Peff?

Deliverables

- Draft decision tree to guide permeability model selection to support PBBM dev to be drafted and shared at BO session
- Draft permeability method "Ladder" wrt level of confidence to support PBBM dev to be drafted and shared at BO session

Breakout Session F: Considerations for model development: data inputs, disposition and absorption parameters, dealing with sparse data	**Speakers:** Tycho Heimbach, Merck & Co. David Turner, Certara Rebecca Moody, FDA **Moderator 1:** Lanyan (Lucy) Fang, FDA **Moderator 2:** Cordula Stillhart, Roche **Scribe 1:** Philip Bransford, Vertex **Scribe 2:** Xiaojun Ren, Novartis

Q1. What is the best practice for modelling the kinetics of disposition in the absence of IV PK data?

Deliverable: Decision tree for estimating tissue distribution and clearance depending on the type of human PK data available

Questions to the audience while discussing the decision tree:

- What rationale is used for generating IV data during development? Is there an association with compound properties (e.g., BCS class)?
- Any examples of accepted cases of disposition models developed using oral solution data?
- What model use could still be reasonable if the level of validation of the disposition model is limited (e.g., no IV data available)? E.g., support justification of dissolution method selection, support decisions by de-risking certain approaches via modeling, relative comparison of exposures, etc.
- How are PBPK models in animals used during development? What level of confidence/experience is there with transferring parameters from animal PBPK models to human?
- Is it reasonable to generate confidence in animal PBPK before moving to humans?
- At which stage of development are human PBPK models typically developed?
- How do companies handle the situation when IV data and rich PK data are missing?

Q2. What are the criteria and acceptable thresholds for validation of the disposition model?

Deliverable: Guidance on acceptable criteria and thresholds for model validation

Validation requirements may be more stringent (especially for regulatory purpose) when there are more uncertainties

Confidence in disposition model (and thus overall PBBM) depends on the type of data available for model development:

- Decreasing confidence from left to right in the decision tree (IV > oral solution/BCS1/high F > other oral PK > animal PK)
- More justification/rich datasets are required from left to right

Q3. What is a suitable dataset for disposition model development and validation? (e.g., variety of PK profiles in terms of species, formulations, route of administration, dose(s), time distribution of PK sampling, number of subjects, etc.)

Deliverable: Guidance on an acceptable quality of data for disposition model development and verification

Breakout Session G: Considerations for model validation, model acceptance/verification criteria in PBBM in view of available clinical data and model risks (impact and consequences)	**Speaker:** Min Li, FDA **Moderator 1:** Shereeni Veerasingham, HC **Moderator 2:** Nikunj Patel, Certara **Scribe 1**: David Sperry, Eli Lilly **Scribe 2:** Hansong Chen, FDA

Q1. for Model Verification

Assessment of model structure/components to evaluate correct implementation of model assumptions.

a. Do the model components adequately capture key mechanisms related to in vivo absorption and disposition processes for the product/drug?
   - Are the model assumptions justifiable and fit for the intended application of the model?
   - Assumptions may relate to disintegration, dissolution, precipitation, degradation, transport, first-pass effect, distribution, and clearance.

b. What approaches, data, and/or information can be used to justify the assumptions?
   - datasets for initial model development and refinement
   - verification of predictive performance using dataset not used in model development
   - parameter sensitivity analysis
   - verification of relevant virtual population

Q2. for Model Validation

Assessment of the predictive performance of the model in comparison to observed in vivo data.

a. What are the main considerations when evaluating the predictive performance of a PBBM?
   - regulatory context of use, model risks (i.e., impact of model simulations on regulatory decision making and consequence), study population, robustness, reliability
   - what justification should be provided to use the model for a different application?
   - is validation with batches that only exhibit “acceptable” performance adequate?
   - can certain bottom-up, mechanistic models be used without validation? e.g., a model for tablet compression force of a long half-life drug where there’s low risk of impact on PK

b. What are appropriate model validation targets and acceptance criteria?
   - targets and criteria specified a priori

- comparisons of the predicted and observed in vivo drug concentration versus time profiles as well as PK parameter estimates, e.g., Cmax, Tmax, and AUC
- statistical analysis of PK parameters: percent prediction error (%PE), average fold error (AFE), absolute average fold error (AAFE) or average absolute prediction error (AAPE%)
- benchmark for model validation; is a comparison of average profiles sufficient?
- mispredictions/failure to meet acceptance criteria and impact on model use

c. How should uncertainty in parameters of interest be evaluated?

- perform parameter sensitivity analysis to characterize the influence of uncertain parameters on model outcome; if influence is minimal, use a suitable value within the range
- reduce uncertainty of influential parameters: if influence is high, further characterization of the parameter with suitable experiments or independent validation of the assumed value on another clinical data set could be used to evaluate suitability of the uncertain parameter

Breakout Session H: **Considerations for model application: VBE trials vs. single representative modeling, dealing with within and between subjects variability and parameter uncertainty**	**Speakers:** Amin Rostami, Univ of Manchester Viera Lukacova, Simulations Plus **Moderator 1:** Duxin Sun, Univ of Michigan **Moderator 2:** Jean-Flaubert Nguefack, Sanofi **Scribe 1:** Tessa Carducci, Merck & Co **Scribe 2:** Manuela Grimstein, FDA

Q1. Intra- or inter-subject variability? Which one is larger?

Q2. How to model intra- or inter- subject variability?

Q3. What is the cut off value for intra- or inter-subject variability, acceptable for VBE vs. single representative model?

Q4. Parameter optimization considering these variability

Q5. What sample size for VBE? What main factors drive the VBE sample size estimation?

If time permits

Q6. If VBE is comparing dosage strengths (for instance 120 mg versus 2 x 60 mg) and the baseline model for 2 x 60 mg was built using Johnson dissolution mode with PSD data, how to proceed if we don't have a biopredictive dissolution method mimicking the drug dissolution process in vivo?

Q7. By having a biopredictive dissolution method mimicking the drug dissolution process in vivo, is it necessary to compare the simulated Cp-time profile of reference strength using both the models Johnson and biopredictive dissolution data even if f2 value >50 in the biopredictive dissolution?

Breakout Session I: **Considerations for model application: Establishing safe space and failure edges, non-BE batches and alternative IVIVR/C**	**Speakers:** Xavier Pepin, Simulations Plus Konstantinos Stamatopoulos, GSK Siri Kalyan Chirumamilla, Certara **Moderator 1:** Haritha Mandula, FDA **Moderator 2:** Rob Ju, AbbVie **Scribe 1:** Michael Wang, Merck & Co **Scribe 2:** Joan Zhao, FDA

Q1. Which biopharmaceutics properties of the drug substance are critical to and should be considered to establish a model for safe space? That is, are there any red flags in a drug's biopharmaceutics properties (active transporter, regional absorption, precipitation, etc..) that could affect model development for safe space? In such case, if PBBM/IVIVCR cannot be developed, how would alternative model such as non-linear IVIVC (or others) be used? How would non-compendial in vitro methods that assess these red flag properties be used?

Q2. What tools (models, data, etc..) are available to detect/avoid an undesired outcome from BA studies designed to establish safe space where model cannot be developed (due to properties of the API and/or drug product) and formulations tested are non-BE to the reference?

Q3. In principle for IR formulations of BCS III/IV molecules, dissolution is not likely to affect in vivo performance as long as the release rate is not too slow, and the probability of achieving BE of tested formulations is high. Thus, it is supposed to make it more feasible (than BCS I/II) to develop a safe space, even when a model cannot be developed. However, while it is desired, we lack the ability to reliably predict a threshold of drug release rate beyond which in vivo performance is expected similar (BE is expected and safe space is identified as long as drug release rate is greater than the threshold). How can models (or other tools) be used to establish the threshold of drug release rate to establish the safe space and "failure edge' for low-permeability drug molecules.

Q4. Related to question Q3, for BCS I/II molecules, dissolution likely affects in vivo performance and non-BE results from tested formulations is more likely than BCS III/IV molecules. A safe space can still be developed as long as a model is available. However if a model is not possible, we run the risk of conducting BA studies without a clear safe space. One mitigation option is to perform iterations of BA studies to find a formulation that is right on the failure edge of BE. Nevertheless, if this occurs, more than one BA study are likely required, and outcome is still uncertain. Under this circumstance, what alternative models (tools) can be used to help establish the safe space?

Q5. Larger formulation variations which likely lead to non-BE results are often required to establish a safe space. However, a key criterium of testing formulation variations is these variations do not alter drug release mechanism or else it may result in unexpected in vivo performance and/or compromise the development of a model. What data are needed to support the maintenance of release mechanism?

Q6. Depending on the properties of API, formulations/processes, and in vitro methods, it is possible a safe space is narrower than ±10%. What mitigation strategies (developing a new in vitro method, etc..) should be considered if this occurs? Better yet, how can modelling/simulation be used to predict this undesired outcome before conducting the BA studies?

Breakout Session K: PBBM in generics drug product development	**Speaker:** Yunming Xu, FDA **Moderator 1:** Yi-Hsien Cheng, FDA **Moderator 2:** Rajendra Singh, Teva **Moderator 3:** Maitri Sanghavi, Certara **Scribe:** Rajesh Savkur, FDA **Scribe:** Martin Hingle, Novartis

This session will discuss on latest advances and challenges of utilizing PBBM and virtual simulation for generic drug development purposes to facilitate formulation design, risk assessment, and to provide scientific evidence and justification to support biowaivers. The session speaker from regulatory agency will present specific cases of using PBPK absorption modeling and virtual simulations to assess bioequivalence (BE), to evaluate the biopredictivity of in vitro dissolution data on in vivo BE studies, to investigate the link between particle size distribution (PSD) and in vivo PK data, to support biowaivers for in vitro and in vivo

studies.

Q1. Optimal Strategies for Developing and Validating Models for Generic Drugs?

- Essential data prerequisites
- Applicability of RLD models to generic drugs
- Under what circumstances is this viable?
- What supplementary measures are required for regulatory decision-making?
- Utilization of data from RLD formulation variants for model validation
- Should RLD formulation variant data (dissolution and corresponding PK) be employed for validation?
- Which approaches are suitable when (1) dissolution methods differ; or (2) variability in PK data is higher for the RLD?
- Scenarios for extending the model to different strengths in generics
- When can the PBBM model be utilized to waive requirements for uncovered strengths in model development and validation?

Q2. Integration of Excipient Substitution: How Can PBBM/PBPK Facilitate Formulation Modifications?

- Approaches of applying PBBM/PBPK modeling to evaluate the impact of critical (problematic) excipients on absorption and BE outcome in drug product development.

Q3. Key Factors to Consider in Establishing a PBBM-Safe Space for Generic Drugs?

- Workflow to establish dissolution safe space in generic drug development.
- Acceptability of comparison of proposed upper and lower dissolution specifications with exhibited batch dissolution data versus comparing between proposed upper and lower dissolution specifications.
- Perspective from PSD specifications.

Q4. Application of developed and validated PBBM to support generic drug development, to provide scientific evidence and justification, to support biowaivers for fed BE studies, and to establish biorelevant dissolution specifications.

Example 1: Application of validated model to predict the gender impact on BE to support the waiver of incorporating females in BE studies – Best practices, decision tree and way.
Example 2: Possibilities of implementing PBPK model and virtual BE simulation to justify for including/excluding outliers in BE study, specifically when the outlier is due to reference formulation behavior?

Q5. Challenges, potential solutions, and successful experiences (e.g., PSD for API) in developing biopredictive PBBM from both regulatory agency and industry perspectives.

Breakout session L: Virtual BE applications	**Speaker:** Amitava Mitra, Kura Oncology **Moderator 1:** Andrew Babiskin, FDA **Moderator 2:** Amitava Mitra, Kura Oncology **Scribe 1:** Parnali Chatterjee, FDA **Scribe 2:** Erik Sjögren, Pharmetheus

Q1. What are the experiences and challenges in applications of VBE in Post-approval changes? e.g., excipient changes for BCS 3 drug products BE

Q2. What are the criteria for selecting populations for VBE simulations (in terms of number, sex, demographics, disease state)?

Q3. What are the experiences, successes, considerations, and challenges in applying VBE to pediatric population?

Q4. What are your experiences with regulatory acceptance of VBE based specification justifications (e.g., dissolution, API PSD)? What are feedback(s) on the model?

Q5. Should non-BE batch be a requirement for VBE verification? What are the challenges? What are other potential options for model verification?

Breakout Session M: Safe Space & extrapolation	**Speaker:** Sandra Suarez-Sharp, Simulations Plus **Moderator 1:** Kimberly Raines, FDA **Moderator 2:** Sandra Suarez-Sharp, Simulations Plus **Scribe 1:** Kevin Wei, FDA **Scribe 2:** André Dallmann, Bayer

Q1. Most safe space applications involve interpolating between non-BE and BE batches. Nevertheless, the production of non-BE batches might pose challenges.

a. Under what circumstances could one predictively extrapolate to the non-BE region (without clinical data from a non-BE batch)?
b. If the dissolution safe space is narrowed, what information could aid in expanding its boundaries?
c. Is it feasible to apply a safe space developed for an IR formulation to other IR formulations?

Q2. Expanding the dissolution safe space to encompass other specifications (e.g., particle size, formulation adjustments, manufacturing changes):

a. What kind of data or methods are necessary to extend the safe space to those Critical Material Attributes (CMAs) or Critical Process Parameters (CPPs) not utilized in creating/validating the safe space?
b. What considerations are relevant for a PBBM safe space when dealing with formulations containing modifying/functional excipients like cyclodextrins, sorbitol, acidifying agents, etc.?

Q3. When constructing a dissolution safe space, what should serve as the reference?

a. What constitutes the internationally accepted definition of safe space?

Q4. Approaches to maintaining a PBBM for establishing a safe space across the product life cycle:

a. How could a safe space be utilized to attain flexibility post-approval?
b. Although a Regulatory Authority might accept a dissolution test and specification, will they communicate to an applicant that they have indeed "approved" a safe apace along with the permissible post-approval flexibilities?

Q5. What information is needed in a regulatory submission to establish a safe space?

a. What is the minimum data needed to formulate a safe space for innovator compared to generic drugs?

If time permits

Q8. Which models should preferably be used when building a safe space (empirical vs. semi-mechanistic)

Q9. Which strategies toward building a safe space should be adopted when precipitation is observed in vitro? Can a safe space be built in this situation?

Q10. Which in vitro assay is typically chosen for the development of a safe space via PBBM (USP II, USP IV, two stage assay etc.)?

Q11. Typically, PBBM is validated across numerous clinical studies. Which steps can be taken when the 10% PE criterion for PBBM validation required per guidance is not met for a specific, independently conducted, clinical study?

Breakout Session N: Regional absorption & MR PBBM applications	**Speaker:** Rebecca Moody, FDA **Moderator 1:** Anitha Govada, FDA **Moderator 2:** Christer Tannergren, AstraZeneca **Scribe 1:** Anders Lindahl, Swedish MPA **Scribe 2:** Sherin Thomas, FDA

Q1. Current applications of PBBM for MR formulations – Confidence & room for expansion?

a. What is the usefulness/confidence of PBBM for alcohol induced dose dumping and food predictions for MR formulations? Waive in vivo studies?
b. What are the considerations when establishing PBBM for MR product? Does the release mechanism impact the strategy of building PBBM for MR products?

Q2. How to account for regional/colon absorption in PBBM for ER formulations - Current status and how to improve

a. What factors impact regional absorption and should be incorporated in model development and validation?

Q3. Which modeling approach is more feasible for MR product, traditional IVIVC or PBBM?

a. How to best incorporate mechanistic absorption modeling with IVIVC, i.e., PB-IVIVC

Q4. What is the best approach for integrating in vitro dissolution data into PBBM for MR products?

a. What is the suitability of non-mechanistic vs mechanistic dissolution integration approaches (e.g., Weibull to Z-factor to extended Wang-Flanagan)?
   i. What are the limitations in model applicability based on integration of in vitro dissolution (i.e., does empirical parameterization of the in vitro release rate decrease our confidence in the model's ability to predict/simulate population exposure in vivo?)

Q5. Considerations for higher quality of in vitro data inputs into PBBM for more reliable in vivo PK predictions and formulation performance comparisons

a. Bile salt solubilization ratio considerations for PBBM of Modified Release Dosage forms

Q6. What is an appropriate prediction performance for ER models?

a. What criteria should be evaluated (C_{max}, AUC, T_{max}, Partial AUCs, etc.) and how should it be evaluated (AFE, PE, AAFE, etc.)?