WORKSHOP

Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls

September 23-25, 2019

College Park, MD

Background

The role of biopharmaceutics in drug development is to ensure that drug release and absorption from the drug product results in optimal therapeutic efficacy and safety for the patient. As such, understanding the drug release mechanism and *in vivo* factors affecting the rate and extent of drug release are critical.

The assumption generally works that two presentations of the same active drug moiety which deliver similar drug concentrations at the site of action (either systemic or local) can be considered as similarly efficacious. Therefore, the local and systemic exposure of drugs is a primary aspect of biopharmaceutics. In this regard, several FDA guidance documents[1,2,3] advocate the use of biopharmaceutics tools such as *in vitro* dissolution, bioavailability (BA)/Bioequivalence (BE) assessment along with modeling and simulation approaches as the means to support drug product quality (e.g., following formulation and manufacturing changes) and as an aid to support regulatory decisions.

The advancements in science as well as modeling and simulation tools during the last decade now enable the development and application of physiologically based models which link physiological and physicochemical factors to assist drug development and regulation. In this regard, physiologically based pharmacokinetic (PBPK) modeling approaches have become a key tool to predict systemic exposure of the drug product[4]. However, the typical inputs for current PBPK models only account for rudimentary properties of the formulation. Detailed assessment of compositional variations, manufacturing changes and the resulting formulation performance are not adequately translated into the current PBPK models, and thus it is challenging to predict

the effect of such changes on local and systemic exposures in human. Thus, there is a need for the refinement of existing approaches (e.g. PBPK modeling) with a focus on translating the effect of formulation and manufacturing changes (e.g. biopharmaceutics analysis) into *in vivo* performance.

Ideally, to assess drug product clinical performance following formulation and manufacturing changes, biopharmaceutics models that capture the interactions between the physiology (i.e., by using physiologically based models) and the pharmaceutical formulation by mechanistic implementation of formulation/manufacturing aspects that are relevant to dissolution/release from the drug product are critical. Such models, namely physiologically based biopharmaceutics models (PBBM) should take into consideration factors beyond physiological and pharmacokinetic (i.e. ADME) components. They should define mechanistic elements of drug dissolution/release relevant to interactions of the pharmaceutical product with physiological conditions and events which can be parameterized to describe the key formulation characteristics. Once these mechanistic elements are defined, PBBM modeling can be used to predict the impact of variations in the critical material attributes (CMAs) and critical process parameters (CPPs through the establishment of a safe space via either IVIVCs or *in vivo-in vitro* relationships (IVIVRs) combined with virtual BE simulations. This approach will facilitate the incorporation of clinical relevance in product quality from initial development through marketing approval to lifecycle management and thereby minimize the need to conduct additional *in vivo* BE studies, leading to reducing cost in product development and supporting regulatory decisions.

Scope of the Workshop:

This workshop is designed to identify and start to fill the gaps in knowledge on the use of PBPK approaches for drug product quality (e.g., in vivo impact of manufacturing changes). Novel and evolving approaches to develop biopredictive dissolution methods should be delineated and best practices for PBBM model development and verification/validation should be identified.

The scope of the workshop includes:

1. Identifying biopharmaceutics and modeling tools to facilitate formulation development and to enhance risk management of bioperformance over the product's entire life cycle;
2. Demonstrating the rewards and challenges of coupling biopredictive dissolution testing with translational PBPK (i.e. PBBM); and
3. Providing an opportunity for direct dialogue between Regulatory, Industry and Academic stakeholders to identify the gaps in knowledge and path for collaboration to move the field forward.

To achieve these objectives, in addition to podium presentations ample time is allocated for discussion (i.e., breakout (BO) sessions).

Deliverables

A. Identify and discuss the gaps among in vitro studies, relevant in vivo studies, and current modeling tools (e.g. PBPK) including a discussion of their advantages and remaining challenges:
    1. Identify and list the relevant physicochemical properties and physiological variables governing the *in vivo* absorption rate (with a focus on low solubility compounds)
        a. Identify best practices for measuring equilibrium and kinetic solubility
        b. Discuss which of these is more relevant for PBBM purposes
    2. Biopredictive dissolution method development, a key element for successful PBBM
        a. Identify best practices for single media dissolution experiments

b. Discuss how to measure supersaturation, precipitation rate and induction times for APIs and formulations and integrate those into a PBPK model
c. Identify approaches to incorporate the influence of common ion effects and local pH on dissolution into commercial software).
d. Identify approaches to transition from biopredictive to QC dissolution methods when these need to be different.
    i. The use of biorelevant media for projecting the *in vivo* solubility and its value in the development of biopredictive dissolution methods
    ii. The development of biopredictive dissolution methods to reflect *in vivo* hydrodynamic conditions
    iii. Translation of Biorelevant methods into QC: when and how?
e. Describe approaches to input dissolution into the absorption model for immediate release or prolonged release formulations. Discuss the mechanistic and non-mechanistic models, and their advantages or limitations

3. Identify and list the challenges and limitations of currently available PBPK approaches for modeling the clinical impact (i.e. systemic exposure) of formulation and manufacturing changes.
    a. Identify possible paths forward for modeling in vitro dissolution/release as a surrogate for overall drug product performance following manufacturing changes and its interaction with the in vivo environment.
4. Identify and list best practices for PBBM development, verification and validation.
    a. Discuss the impact of input parameters, criteria for selection, model assumptions, and parameter estimation strategies
    b. Discuss the value of parameter sensitivity analysis (when and how)
        i. Advantages and disadvantages of global sensitivity analysis vs. local sensitivity analysis
    c. Establish a path towards parameter optimization (when, how and goodness of fit criteria)
    d. Identify suitable criteria to define successful prediction

e. Discuss ways of investigating the impact of population variability for model validation purposes (should average population data or individual data be used, implementation of biomarkers and ways forward in the absence of these)

5. Application of PBBM in support of product quality (e.g. manufacturing changes): the value of virtual BE and data needed to justify its application.
6. Identify the appropriate terminology for the application of physiologically based biopharmaceutics modeling and simulation to drug product quality.
7. Provide ample opportunities for direct dialogue between Regulatory, Industry and Academic stakeholders
    a. What are the applications of PBBM and in which concrete applications do these support flexibility in regulatory assessment (e.g., reducing the need for human experimentation)?
    b. What is the situation in the US compared to the rest of the world?
    c. What are the perceived hurdles for application of PBBM to support quality decisions and clinically relevant specifications setting in the medium and long term and what actions are needed to promote its use?

B. Preparation of a White Paper that summarizes the workshop outcomes.

DAY 1 AGENDA

In vitro Biopredictive Methods

Moderators: Jennifer Dressman (Goethe University), Xavier Pepin (AstraZeneca) and Poonam Delvadia (FDA)

Time	Speaker	Topic
8:30-8:40 am	Sandra Suarez (FDA)	Welcome and objectives of the Workshop
8:40-9:10 am	Paul Seo (FDA)	The Impact and future of PBBM in Support of Drug Product Quality
9:10-9:40am	Lynne Taylor (Purdue University)	Approaches to measure equilibrium (intrinsic) and kinetic solubility, and the impact on dissolution and membrane transport kinetics
9:40-10.10 am	Jennifer Dressman (Goethe University)	The value of biorelevant media for measuring solubility and in the development of biopredictive dissolution methods.
10:10-10:25 am	**BREAK**	
10:25-10:55 am	Erik Sjogren (Pharmetheus)	Measurement and prediction of human permeability: current best practices, regional differences and future developments
10:55 – 11:25 am	James Butler (GlaxoSmithKline)	Biopredictive dissolution methods with a view to integration in PBPK
11:25-11:55 am	Ed Kostewicz (Goethe University)	In vitro approaches to understanding supersaturation and precipitation of weak bases and enabling formulations
11:55-12:45 pm	LUNCH	
12:45-1:15 pm	Mirko Koziolek (University of Greifswald)	The importance of hydrodynamics in the development of biopredictive dissolution methods.

1:15pm-1:30 pm	Introduction and expectations of BO sessions	**Xavier Pepin (AstraZeneca)**
1:30-1:45 pm	Break/transition to BOs	
1:45-3:45 pm ***BO session A***	Best Strategies for Determining Solubility, Supersaturation and Critical Supersaturation	**Moderators:** Om Anand (FDA); James Butler (GSK) **Scribes**: Jennifer Dressman (Goethe U); Lynne Taylor (Purdue University)
1:45-3:45 pm ***BO session B***	Best strategies for the development of biopredictive (clinically relevant) dissolution methods, a key element for successful modeling and simulation	**Moderators:** Bertil Abrahamsson (AstraZeneca); Poonam Delvadia (FDA) **Scribes**: Andre Dallmann (Bayer AG); Filippos Kesisoglou (Merck & Co., Inc.)
1:45-3:45 pm ***BO session C***	Gastrointestinal (GI) Systems Parameters (mucus, volume, motility): Where are the pitfalls and how to overcome them?	**Moderators**: Yang Zhao (FDA), Mirko Koziolek (U of Greifswald) **Scribes**: Xavier Pepin (AstraZeneca); Ed Kostewicz (Goethe U)
1:45-3:45 pm ***BO session D***	Permeability along the GI tract. Translation from biopharmaceutical measurement to a model parameter?	**Moderators**: Xinyuan Zhang (FDA), Erik Sjorgen (Pharmetheus) **Scribes**: Neil Parrott (Roche); Andrew Babiskin (FDA)
3:45-4:30	Coffee break/moderators and scribes to convene	
4:30-5:15 pm	Summary of Breakout discussions	**Lead Moderators**
5:15-6:00 pm	Discussion	Organizing Committee (OC) members/speakers/moderators/scribes

DAY 2 AGENDA

Best Practices for Model Development, Verification, and Validation

Moderators: Neil Parrott (Roche) and Sandra Suarez (FDA)

Time	Speaker	Topic
8:30-8:35 am	Sandra Suarez (FDA)	Introduction and logistics
8:35-9:05 am	David Good (Bristol-Myers Squibb)	Opportunities and challenges for modeling the clinical impact (i.e., systemic exposure) of formulation and manufacturing changes.
9:05-9:35 am	Christian Wagner (Merck Healthcare KGaA)	Best practices in model development: input of solubility, supersaturation, precipitation and permeability.
9:35-10:05 am	André Dallmann (Bayer AG)	Best practices for model building: parameter optimization, sensitivity analysis and how to assess the match to clinical data
10:05-10:20 am	BREAK	
10:20-10:50 am	James Mullin (Simulations Plus)	Translating the effect of product manufacturing variants from in vitro to the clinic. Current possibilities and gaps for IR formulations.
10:50-11:20 am	Nikunjkumar Patel (Certara)	Translating the effect of product manufacturing variants from in vitro to the clinic. Current possibilities and gaps for ER formulations.
11:20- 11:50 am	Filippos Kesisoglou (Merck & Co., Inc.)	Approaches for entering dissolution into the absorption model, reasons for selection, model assumptions, and parameter estimation strategies.
11:50-12:35 pm	LUNCH	
12:35 pm- 1:05 pm	Arian Emami Riedmaier (AbbVie)	Considerations for qualification and verification of models
1:05 pm-1:35 pm	Amitava Mitra (Sandoz)	Impact of population variability (intra and inter) and sample size for model validation and data needed to justify application of virtual BE.

1:35pm-1:50 pm	Introduction and expectation of BO sessions	Neil Parrott (Roche)
1:50: 2:05 pm	Break/transition to BOs	
2:05-4:05 pm ***BO session A***	Challenges to predict effects of drug product attribute changes (e.g. particle size distribution changes) on dissolution and in vivo performance using in silico models. Are the tools ready?	**Moderators:** Sandra Suarez (FDA), Filippos Kesisoglou (Merck & Co., Inc.) **Scribes:** Kimberly Raines (FDA); James Butler (GSK)
2:05-4:05 pm ***BO session B***	Strategies to handle parameter uncertainty and variability within and between subjects.	**Moderators:** Maziar Kakhi (FDA); Neil Parrott (Roche) **Scribes:** David Good (BMS); Nikunjkumar Patel (Certara)
2:05-4:05 pm ***BO session C***	Best practices for model development and verification and criteria for defining prediction success.	**Moderators:** Min Li (FDA); Xavier Pepin (AstraZeneca) **Scribes:** Arian Emami Riedmaier (AbbVie); James Mullin (Simulations Plus)
2:05-4:05 pm ***BO session D***	Approaches to establish sameness following manufacturing/formulation changes: Advantages and disadvantages of Virtual BE.	**Moderators:** Eleftheria Tsakalozou (FDA); Amitava Mitra (Sandoz) **Scribes:** Christian Wagner (Merck Healthcare KGaA); Yang Zhao (FDA)
4:05-4:45 pm	Coffee break/ Moderators and scribe to convene	
4:45 pm- 5:30 pm	Summary of Breakout Sessions	**Lead Moderators**
5:30-6:15 pm	Discussion	OC members/speakers/moderators/scribes

DAY 3 AGENDA

Applications to PBBM to support Drug Product Quality

Moderators: Amitava Mitra (Sandoz) and Andrew Babiskin (FDA)

Time	Speaker	Topic
8:30-8:35am	Andrew Babiskin (FDA)	Welcome and Logistics
8:35-9:05am	Yang Zhao (FDA) and Sandra Suarez (FDA)	FDA expectations in building a safe space to gain regulatory flexibility based on PBBM
9:05-9:35 am	Evangelos Kotzagiorgis (EMA)	EMA expectations in building a safe space to gain regulatory flexibility based on PBBM
9:35-10:05 am	Neil Parrott (Roche)	**Case Study:** Application of PBBM in risk assessment of effect of acid reducing agents (ARA) on PK and formulation development
10:05-10:20 am	BREAK	
10:20-10:50 am	Satish Sharan (FDA)	Prediction of Human Pharmacokinetics Utilizing In Vitro Chewing Method and PBPK Analyses for Abuse-Deterrent Hydrocodone Bitartrate Extended Release Tablets
10:50-11:20 am	Christophe Tistaert (Janssen)	Bridging physiology-based dissolution testing to QC testing using PBBM
11:20-11:50 am	Xavier Pepin (AstraZeneca)	**Case Study:** The use of PBBM and biomarkers to provide detailed mechanistic understanding of in vivo dissolution and absorption. An industrial example
11:50-12:40 pm	**LUNCH**	
12:40- 1:10 pm	Tycho Heimbach (Novartis)	**Case Study:** A Physiologically Based Biopharmaceutics Modeling for Food Effects – Possibilities and Opportunities
1:10-1:25 pm	Introduction and expectation of BO sessions	Amitava Mitra (Sandoz)
1:25: 1:40 pm	**Break/transition to BOs**	

1:40-3:40 pm **BO session A**	Discussion of several terminologies related to physiologically based pharmacokinetics modeling in support of drug product quality (e.g., physiologically based biopharmaceutics modeling).	**Moderators:** Banu Zolnik (FDA); Erik Sjogren (Pharmatheus) **Scribes:** Tycho Heimbach (Novartis); Fang Wu (FDA)
1:40-3:40 pm **BO session B**	Risk-based approach in the development and implementation of PBBM modeling to support drug product quality and clinically relevant specifications setting	**Moderators:** Vidula Kolhatkar (FDA); Shefali Kakar (Novartis) **Scribes:** Xavier Pepin (AstraZeneca); Min Li (FDA)
1:40-3:40 pm **BO session C**	The Road towards harmonization among regulatory agencies on evidentiary standards for PBBM	**Moderators:** Shereeni Veerasingham (Health Canada); Shinichi Kijima (PMDA); Baoming Ning (NIFDC); **Scribes:** Greg Rullo (AstraZeneca); Evangelos Kotzagiorgis (EMA); Kimberly Raines (FDA)
1:40-3:40 pm **BO session D**	Strategies for bridging biorelevant and QC dissolution via PBBM	**Moderators:** Sandra Suarez (FDA); Christophe Tistaert (Janssen) **Scribes:** Poonam Delvadia (FDA)**;** Jennifer Dressman (Goethe U)
3:40-4:30 pm	Coffee break Moderators/scribes to convene	
4:30- 5:15 pm	Summary of Breakout Sessions	Lead Moderators

4:15-5:30 pm	Conclusions/Next steps	TBD
5:30-6:00 pm	Discussion	OC members/speakers/moderators/scribes

[1] Dissolution guidance 1997
[2] IVIVC guidance 1997
[3] SUPAC guidance
[4] Kostewicz, E.S., et al., PBPK models for the prediction of in vivo performance of oral dosage forms. Eur. J. Pharm. Sci., 2014. **57**: p. 300-321.