In vivo predictive dissolution and simulation workshop report: Facilitating the development of oral drug formulation and the prediction of oral bioperformance

Yasuhiro Tsume[1*§], Sanjaykumar Patel[2], Nikoletta Fotaki[3], Christel Bergström[4], Gordon L. Amidon[1], James G. Brasseur[5], Deanna M. Mudie[6], Duxin Sun[1], Marival Bermejo[7], Ping Gao[8], Wei Zhu[9], David C. Sperry[10], Maria Vertzoni[11], Neil Parrott[12], Robert Lionberger[13], Atsushi Kambayashi[14], Andre Hermans[9], Xujin Lu[15], and Gregory E. Amidon[1].

[1]College of Pharmacy, University of Michigan, Ann Arbor, Michigan 48109, USA

[2] Merck & Co., Inc., Rahway, New Jersey 07065, USA

[3] Department of Pharmacy and Pharmacology, University of Bath, Bath, UK

[4] Department of Pharmacy, Uppsala University, Uppsala, Sweden.

[5] Aerospace Engineering Sciences, University of Colorado, Boulder, Colorado

[6] Research and development, Lonza, Bend, Oregon

[7] Universidad Miguel Hernández de Elche, Spain

[8] Abbvie, Inc., Chicago, Illinois

[9] Merck & Co., Inc., West Point, Pennsylvania 19486, USA

[10] Eli Lilly and Company, Indianapolis, Indiana 46285, USA.

[11] Department of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece

[12] F.Hoffmann-La Roche, Ltd., Roche Innovation Center, Basel, Switzerland

[13] Food and Drug Administration, Silver Spring, Maryland 21201, USA.

[14] Astellas Pharma Inc., Shizuoka, Japan

[15] Bristol-Myers Squibb Company, New Brunswick, New Jersey 08903, USA.

***Corresponding Author:** Yasuhiro Tsume, College of Pharmacy, The University of Michigan, 428 Church Street, Ann Arbor, MI 48109-1065. Phone: 734-647-2345. Fax: 734-763-6423. Email: ytsume@umich.edu

[§]**Current address:** Merck & Co., Inc. 126 E Lincoln Ave. Rahway, NJ 07065, USA. Phone 732-594-7059. Email: yasuhiro.tsume@merck.com

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Abstract

This summary report for the "*in vivo* predictive dissolution and simulation workshop" highlights presentations from a two-day workshop held on September 11-12, 2017. This workshop was aimed to present scientists at FDA, EMA, industry and academia the most recent advances in dissolution methodologies and scientific knowledge for oral drug products, which could be useful for guiding early phase development, bioavailability (BA) and bioequivalence (BE) studies and Scale-Up and Post-Approval Changes (SUPAC) of oral products. Presentations and discussions focused on appropriate *in vitro* and *in silico* applications and tool selections to predict *in vivo* bioperformance of oral formulations. Product developability and Quality by Design (QbD) would be determined by the physicochemical characteristics of active pharmaceutical ingredients (API), *in vitro* dissolution and *in silico* models/computer simulation. Many methodologies and applications are available to predict *in vivo* bioperformance of oral products/formulations. It is crucial that the selections of appropriate tools based on API and formulations to maximize *in vivo* prediction by *in vitro/in silico* results. This workshop presented cutting-edge tools/methodologies and how to select the right tools from a methodology toolbox and testing parameters to predict best *in vivo* bioperformance of test products. The combinations of *in vivo* minded *in vitro* dissolution methodologies and computational approaches become mainstream to predict oral absorption/plasma profiles of oral products. This workshop provides the degree of advancement within state-of-the-art scientific knowledge, validation, and development and the extent to which the regulatory community

has absorbed and accepted these advancements in science-based mechanistic approaches to oral drug product development.

Introduction

A two-day workshop entitled "*In Vivo* Predictive Dissolution and Simulation" was held September 11-12, 2017 in Washington DC focused on the selection of applications, methodologies, and scientific advancements to predict *in vivo* bioperformance of oral drug products/oral drug formulations based on the active pharmaceutical ingredient (API) and drg product formulation. This workshop was fully sponsored by the AAPS and featured speakers from industry, academia, and regulatory agencies to introduce the state-of-the-art in cutting-edge applications, methodologies and latest initiatives in *in vivo* prediction of oral drug product performance to attendees worldwide. A broad range of dissolution methodologies and simulations together with the determination of developability based on physicochemical characteristics were discussed specific considerations for *in vivo* prediction implementing bioavailability (BA), bioequivalence (BE), and quality by design (QbD), in this two-day workshop.

The objectives of this workshop were to:

- Present scientists at regulatory agencies, industry and academia the most recent advances in dissolution methodologies, computational applications and science for oral drug products to predict *in vivo* behavior of oral drug products, which could be useful for guiding early phase development, bioavailability (BA) and bioequivalence (BE) studies and Scale-Up and Post-Approval Changes (SUPAC) of oral products.

- Present state-of-the-art *in vivo* predictive dissolution methodologies for drug products, including determination *in vitro* testing parameters to achieve *in vivo* predictive and desired outcomes, and how to interpret *in vitro* results and translating them into potential IVIVCs.
- Present state-of-the-art scientific analysis and knowledge using the latest mechanistic BCS-subclass-based *in vivo* and *in silico* predictive dissolution methodologies.
- Present a mechanistic basis for more efficiently reviewing pharmaceutical product change applications and new generic product applications, including BE studies, assuring therapeutic benefits and safety of oral drug products for public health.
- Provide a forum to discuss *in vitro* dissolution and *in silico* simulation through case studies.

Workshop participants learned the newest mechanistic, BCS Subclass based, *in vivo* predictive dissolution methodologies and physiologically-based computer simulation and science, and were presented with discussion on state-of-the-art dissolution methodologies based on physicochemical characteristics of API. Case studies were presented where current quality control (QC) dissolution methodologies have been inadequate predicting *in vivo* performance, and bioequivalence failure. An *in vivo* predictive dissolution could provide mechanistic explanation of *in vivo* results which could help guide an early formulation development effort, bridge scale up work and understand reference product profiles for generic formulation development.

This workshop was targeted to regulatory scientists, pre-formulation, formulation, biopharmaceutics, and QC scientists in industry, and graduate students and scientists in the academia. The workshop focused on presenting the most recent methods and scientific understanding related to possible pharmacokinetic performance and bioequivalence (BE) risk, *in vivo* dissolution/prediction for a test formulation/a test oral product to meet for ensuring the therapeutic efficacy of modified/changed product. Formulation changes occur frequently over the course of an innovator product's lifetime due to composition, manufacturing, and site of manufacturing changes. BE provides an important standard for the development and approval of multi-source and generic drug products, the most rapidly expanding segment of the pharmaceutical industry worldwide. The workshop benefited the audience by presenting the mechanistic basis for more efficiently designing pharmaceutical product/formulation and for quality by design (QbD) studies.

Day 1

In vivo buffers and buffer properties for affecting solubility and dissolution rate.

Dr. Gregory E. Amidon (University of Michigan) led off the conference making the case that the critical link between oral solid dosage form formulation, *in vivo* plasma levels, and therapeutic effect is *in vivo* dissolution. He discussed several key aspects important to the development of relevant *in vitro* methods focusing on our improved understanding of bicarbonate as our primary lumenal buffer. Accurate prediction of dissolution rate requires an understanding of the conditions at the dissolving drug surface (1, 2). For acidic or basic drugs, an *in vitro* measurement of dissolution that reflects *in vivo* conditions requires

dissolution media that yields a surface pH (pH_0) representative of *in vivo* conditions (1-6). The improved understanding of bicarbonate as a buffer is important and confirms that lumenal bicarbonate buffer concentration and buffer capacity is very low and this is critically important to developing methodologies that reflect *in vivo* pH_0 (7). This more comprehensive understanding of *in vivo* hydrodynamic and chemical conditions will allow for physiologically and physicochemically relevant *in vitro* dissolution testing to be performed on a sound, scientific basis.

In Vivo Gastrointestinal Fluid Composition and Effects of Drug Substance Physiochemical Properties on Solubilization

Dr. Christel Bergström (Uppsala University) continued with a thorough presentation of composition of human intestinal fluids. She emphasized that recent clinical studies pointed at a higher pH in the stomach than that typically used in compendial media (median of 2.5 with a range of 1.7-3.3 in comparison to compendial pH of 1.0-1.2), a lower buffer capacity in the upper gastrointestinal tract than previously thought, and a larger intra- and inter-individual variability in bile salts and phospholipids than previously has been reported (7-9). These factors may significantly affect both dissolution rate and solubilization in the human intestinal tract. For this reason, there is not a single biorelevant medium that can be used to provide insights into the expected variability of dissolution rate and solubilization; rather a number of biorelevant media is likely to be needed to provide insights into the expected variability *in vivo*. She then linked the performance of drugs to their physicochemical properties and in particular pointed at the usefulness of understanding the role of lipophilicity, solid state properties and extent of ionization on the dissolution in

144 human intestinal fluids (10, 11). These physicochemical properties will inform on which
145 types of biorelevant media to select for a particular compound. Further, computational
146 modeling was discussed and identified as a tool that merits to be used to predict e.g.
147 dissolution, solubility and biopharmaceutical performance (12). She identified that more
148 clinical data on the impact of the fed state on drug dissolution are warranted to better
149 understand inter-individual variability in the fed state.

150 **Impacts of In Vivo Fluid Hydrodynamics on Dissolution and Absorption in the**
151 **Human Intestines**

152 Dr. James G. Brasseur (University of Colorado) discussed the impacts of intestinal fluid
153 motions ("hydrodynamics") on the processes by which drug molecules are released from
154 clouds of small drug particles from a disintegrated tablet or capsule as particles and
155 molecular concentrations are transported within the intestinal lumen and drug molecules are
156 absorbed at the mucosal surface. Emphasis was placed on the varying impacts of different
157 classes of motility patterns (i.e., changes in luminal geometry along gut segments as a
158 function of time driven by contraction of the muscle fibers within the intestinal wall)
159 associated with the different migrating motor complex (MMC) phases of contraction when
160 the gut is in the fasting state vs. fed state motility. Whereas peristaltic motility in the fasting
161 state drives the transport of residual material from the gut, the dominant function in the fed
162 state is nutrient absorption, associated with segmental motions that locally mix intestinal
163 liquid content in addition to bulk transport by peristalsis. The rate of release of drug
164 molecules from drug particles (dissolution) is modulated by flow patterns that transport
165 thousands of drug particles preferentially within localized regions and by the hydrodynamic

enhancement in the rate of release of molecules from the surface of individual drug particles from flow field characteristics local to the moving particle. Dr. Brasseur described the mathematical framework for single particle dissolution rate and showed that the hydrodynamic enhancement of particle dissolution rate was represented within a normalized molecular flux, historically referred to as the "Sherwood number.". It was shown that this normalized particle flux is at the core of mathematical model formulations for dissolution from clouds of drug particles. Dr. Brasseur then went into a detailed review of recent research into two key hydrodynamic influences on particle dissolution rate (i.e., normalized flux): (1) the convection effect which arises from "slip" velocity between the moving particle and the surrounding fluid, and (2) a "shear-rate" effect that has been recently discovered, quantified and experimentally validated that arises from drug particle spin induced by hydrodynamic shear-rate at the location of the particle. Using a computational fluid dynamics *in vivo* simulation environment in which the particle dissolution model was embedded, Dr. Brasseur showed that the hydrodynamic shear-rate effect creates major enhancements in drug dissolution while the convection effect provides only a minor influence due to the small size of the particles. Additional discussion was presented of the physical processes underlying the balance between release and absorption of ibuprofen *in vivo* in the presence of peristaltic motility and high permeability. This balance involves the interplay between diffusion and hydrodynamic transport of drug from the bulk to the mucosal surface and is strongly impacted by the size (or volume) of the pocket of intestinal liquid in which drug molecules are released and transported.

Dissolution Methodologies and Selection of Study Conditions Based upon Drug Physicochemical Characteristics (BCS subclass) & Dosage Forms

Dr. Deanna Mudie (Lonza Pharma & Biotech) presented a mechanistic approach for selecting *in vitro* dissolution methodologies and testing parameters for designing oral drug product formulations and differentiating them with respect to bioperformance. This approach relies upon first predicting the rate determining steps to *in vivo* absorption based upon the drug substance and product of interest, and an understanding of the complex and heterogeneous gastrointestinal tract. For example, dimensionless numbers (e.g. Do, Dn & Pn) can be used to predict whether a compound may be solubility-permeability, permeability or dissolution rate limited *in vivo* (13, 14). BCS sub-classification can be used together with knowledge of the drug product formulation as a basis for predicting relative extent of gastric to intestinal dissolution (15). To demonstrate this methodology, Dr. Mudie presented a case study of spray-dried amorphous solid dispersions of itraconazole with hydroxypropyl methylcellulose acetate succinate dosed to rats (16). Using a material sparing membrane flux apparatus (17), colleagues at Lonza Pharma & Biotech were able to show that the maximum absorption rate for each formulation rank ordered with membrane flux *in vitro* when the test was set up to be solubility-permeability limited and a biorelevant fluid composition representative of fast rats was selected.

Direct Measurement of In Vivo Dissolution of IR and MR Drug Products in Human GI Tract

Dr. Duxin Sun (University of Michigan) presented the *in vitro/in vivo* data analysis of a human intubation study and the challenge of *in vivo-in vitro* correlation (IVIVC) for the

local acting drugs with the administration of modified release (MR) mesalamine oral formulations, Pentasa, Apriso, and Lialda, along with oral mesalamine solution and an immediate release (IR) ibuprofen formulation. The specialized catheter with 4 aspiration channels allowed the measurement of luminal drug concentrations (18, 19). The idea is to correlate the directly measured drug concentration in the human gastrointestinal (GI) regions and the plasma drug concentration along with the drug dissolution in different GI tract by computational modeling. Results indicated that *in vivo* dissolution of MR mesalamine oral dosage forms were highly variable. Pentasa released mesalamine throughout the GI tract including the stomach, while Apriso released mesalamine between duodenum and jejunum regions. However, Lialda rarely released any mesalamine in first 7 hrs. Those MR formulations exhibited the different drug release profiles *in vivo* and *in vitro*. However, the large amount of unmetabolized drugs was observed in feces, suggesting unreleased and/or undissolved. In ibuprofen studies, high concentration of ibuprofen was observed in the stomach and small intestine at 7 hrs after oral administration (18). With the elevation of gastric pH by the intake of liquid meal (Pulmocare®), higher drug concentration of ibuprofen in the stomach was observed (19). However, the lower C_{max} and delayed T_{max} in the plasma profiles in the fed state were observed compared to ones in the fasted state suggesting the slower gastric emptying time in the fed state. Overall, the challenges are the limited data of *in vivo* dissolution in the different GI sites to validate the *in vitro* dissolution models and *in silico* simulation. It would be a mutually beneficial if the industry, academia and the regulators to collaborate to produce and share more *in vivo* dissolution data.

Interpreting Drug Concentration Profiles in Plasma and Relating Them to In Vitro Dissolution Measurements/In Silico Predictions

Dr. Marival Bermejo (Universidad Miguel Hernández de Elche) presented the exploratory data analysis of a human intubation study with the administration of an immediate release (IR) ibuprofen (weak acid) oral formulation. The specialized manometric catheter with 4 sampling ports allowed the measurement of luminal drug concentrations, pH values as well as intestinal wall motility (19). Results indicated that ibuprofen *in vivo* dissolution depends on luminal pH (7). Additionally, time to the next Phase III wave post dose (TMMC) determined the arrival of most of the ibuprofen dose to the small intestine, consequently longer TMMC is reflected in lower C_{max} and longer T_{max}. Absorption rates estimated from plasma levels by deconvolution showed a good correlation with *in vivo* dissolution i.e. maximal absorption rates corresponded with the maximal ibuprofen concentrations in intestinal lumen. A compartmental (stomach-duodenum-jejunum-plasma) mass transport analysis incorporating TMMC, and pH-dependent dissolution reproduced closely the individual plasma levels and the inter-subject variability. These results confirmed the direct link between intestinal dissolution, luminal solution concentration and systemic absorption thus the impact of gastrointestinal variables as pH and motility in oral absorption. iPD methodologies incorporating these variables in combination with mass transport computational methods are necessary tools to optimize formulation development.

iPD Methodologies – Future

Dr. Gordon L. Amidon (University of Michigan) presented his vision of *in vivo* predictive dissolution (iPD) to the future of Biopharmaceutics and to the implications of oral product development through the evolution of regulations on oral drug products, dissolution methodologies, and technologies to advance the understanding of the human GI physiologies. The improved understanding of complexed human GI physiology and the advancement of technologies allows us to develop the *in vitro* dissolution apparatuses, which are physiologically relevant to the human GI conditions, and the simulation and physiologically based pharmacokinetics modeling for the prediction of *in vivo* dissolution and drug absorption of oral dosage forms. Those movements have revolutionized and will keep advancing the development of drug products, the design of oral drug products, and the bioequivalent (BE) studies. However, the regulatory agencies, academia, and industries should fully collaborate to facilitate this advancement and to validate *in vitro* models and to share limited amount of human permeability and plasma data. The global harmonization will be necessary to promote science based dissolution methodologies and BE standards.

Day 2

A Two-Phase Dissolution-Partition Test for Characterizing BCS II Drugs Products and Establishing IVIVR

Dr. Ping Gao (AbbVie) presented his work in developing a two-phase dissolution-partition test for evaluation of BCS II drug formulations. This method, referred as to the biphasic test, permits dissolution in the aqueous media (with pH alteration) under a non-sink condition and simultaneous partition of the dissolved drug into an organic phase that acts as

an “absorption compartment”. The partition of the drug into the organic phase is driven by the free drug concentration in the aqueous phase and this is to mimic absorption *in vivo*. The theoretical model of the biphasic system was developed to reveal that the physiological relevance of this test method is based on the *in vitro* partitioning rate coefficient, kp, approximates the *in vivo* absorption rate coefficient, ka (20). Three case studies of BCS II drug formulations including ABT-072 (weak acid) (21), ritonavir (weak base) (22), and fenofibrate (23) were reviewed. Their *in vitro* profiles obtained in biorelevant media under the optimal hydrodynamic condition by the biphasic test are closely correlated with relative exposures of these drugs in human subjects. These cases jointly reveal the significant impact of supersaturation upon oral exposure of BCS II drugs and a complex interplay among the dissolution, precipitation, and partition processes that dictates the oral exposure.

BCS IIb Drug Substances in the Gastro-Intestinal Simulator (GIS)

Dr. Yasuhiro Tsume (University of Michigan) presented his work in developing a multi-compartment transfer system, gastrointestinal simulator (GIS), to evaluate the bioperformance of weakly base drugs, ketoconazole and dasatinib as model drugs (24, 25). The GIS, which consists of three chambers, gastric, duodenal, and jejunal compartments with secretion chambers to supply appropriate media back into the gastric and duodenal chambers (26). Using the GIS, Dr. Tsume demonstrated the occurrence of supersaturation and precipitation of BCS class IIb drugs and the enhanced absorption resulting from supersaturation effects by the combination study of infusion study and the

dissolution study and the potential to predict clinical outcome with *in vitro* dissolution methods (24, 25). Dr. Tsume mentioned the importance of experimental conditions like aqueous volume (volume to the dose), buffer species, buffer capacity, buffer pH and gastric motility (gastric emptying rate and transit time) with experimental examples (27-30). He also demonstrated the presence of absorption phase (biphasic setting) would be useful in the dissolution methodologies for certain drugs for more accurate *in vivo* prediction (31).

Multicompartment Transfer Model to Predict Dissolution/Precipitation of Weakly Basic Drug

Sanjaykumar Patel and Wei Zhu (Merck & Co., Inc., Kenilworth, NJ, USA) presented their work in developing a multi-compartment transfer system for evaluation of dissolution and precipitation of weakly basic drugs during the transfer out of the stomach into the intestine. This transfer system includes a "gastric" compartment, an "intestinal" compartment, a "sink" compartment for removal of the drugs from intestinal compartment, and a "reservoir" compartment to re-supply FaSSIF media during the course of the experiment. An *in silico* model was built to simulate the time-dependent dissolution and precipitation processes when drugs/formulations were tested using the transfer system, and the precipitation rate obtained from the model was used as the inputs for subsequent absorption modeling. Two case studies, dypyridamole and ketoconazole, were reviewed, as the *in vitro* dissolution and precipitation of these two drugs were analyzed using both transfer system and traditional two-stage dissolution. Using the fitted precipitation rate from transfer system as the inputs for Gastroplus™ modeling, the predicted

pharmacokinetic profiles of orally dosed IR formulations were generally in agreement with observed clinical data. A sensitivity analysis on *in vivo* precipitation in Gastroplus™ suggested an optimal prediction accuracy when precipitation rates from the transfer system was utilized. These case examples showed promising results to support this integrated *in vitro/in silico* transfer system as an alternative approach to estimate in vivo precipitation in intestinal compartment, which is one of the critical attributes for prediction of clinical bioperformance for weak basic compounds.

BCS II/IV Drug Substances in the Artificial Stomach Duodenum (ASD) System

Dr. David C. Sperry (Eli Lilly and Company) presented his work in artificial stomach and duodenum (ASD) as a tool to develop oral drug products. This dissolution apparatus, which mimics the dynamic conditions of the human GI tract, helps predict the *in vivo* impact of oral dosage forms properties such as salts, solid forms, formulation composition, and particle size. The goal of this approach is to reduce the number of animal studies required during formulation development while selecting the best possible oral dosage forms for clinical studies. Certain drugs would supersaturate, precipitate, and/or dissolve in the duodenal region, which have impact on their absorption. Those molecule/formulation related phenomena can be captured by ASD, which mimics the dynamic GI conditions, to support the *in vivo* prediction. The drug concentration in the duodenal chamber of ASD can be predicted based on the drug concentration in the gastric chamber of ASD. The difference between experimental results and calculated/expected results indicates additional dissolution and/or precipitation, which will provide tremendous helps to understand the *in vivo* dissolution and the potential problems of test drug/formulation. Dr. Sperry presented a

few case studies with the different API forms (free base form vs. salt form), the different dosage strengths (low vs. high), the different pH and buffer viscosity to demonstrate the impact of *in vivo* dissolution of test oral formulations. He demonstrated through those case studies that those *in vitro* dissolution profiles obtained with ASD combination of *in silico* absorption model, gCOAS, predict better *in vivo* performance and, hence, the usefulness and practicality of *in vivo* predictive dissolution methodology, ASD.

Implementing In Vitro Dissolution Data into PBPK Models for Evaluation of Absorption from the Lower Intestine

Dr. Maria Vertzoni (National and Kapodistrian University of Athens) presented the impact of absorption from the lower intestine on plasma pharmacokinetic profile. After oral administration of a drug product, the drug absorption from the lower intestine was of particular interest when considering the development of modified release products. It could also be useful, for understanding the pharmacokinetic performance of poorly soluble active pharmaceutical ingredients (APIs), BCS Class II and Class IV APIs, when those are administered in immediate release products and their drug absorption is incomplete in the upper intestine. For the evaluation of colonic absorption, knowledge of drug solubility and dissolution rates in the region is required but relevant estimations remain problematic, due to limited information on the conditions prevailing in the lower intestine. In recent years our understanding on the environment in the lower intestine has been increased (32, 33).

Dr Vertzoni presented the usefulness of biorelevant in vitro data in PBPK models describing oral absorption from upper / middle as well as from lower intestine with various case examples.

She presented the media simulating the contents of lower intestine i.e. distal ileum and proximal colon under conditions simulating the bioavailability and bioequivalence studies in

the fasted and in the fed states and a recently developed in vitro two-stage single-compartment models for evaluating dissolution characteristics in the lower intestine. This approach evaluates the impact of dilution of ileal contents as they empty into the proximal colon and the potential precipitation of weak acids, due to the decrease of the pH in the proximal colon, particularly apparent in the fed state (34-36). To evaluate the importance of specific luminal characteristics within a specific region of intestinal lumen two levels of simulation of luminal composition were considered. Level I biorelevant media reflect luminal pH and buffer capacity whereas Level II biorelevant media take additionally into account luminal bile components and osmolality (35, 36). In addition, the importance of solid particles [i.e. of Level III simulation] was evaluated (36). For the evaluation of the impact of passive absorption from the lower intestine on the overall absorption process, in vitro dissolution data collected under conditions simulating the environment in the upper gastrointestinal lumen and under the conditions simulating the environment in the lower intestinal lumen were coupled with physiologically based oral absorption modelling to simulate the overall drug absorption process.

Based on data collected using high dose low solubility APIs and a colon targeting product, dissolution characteristics in the lower intestine can be much different from that in upper intestine with potential impact on PBPK modelling.

Dr Vertzoni concluded that in situations where stress effects are not expected to be of an issue (e.g. for immediate release products, pellets, products coated with pH sensitive polymers) Level II or even Level I (if API is not very lipophilic) biorelevant media in conjunction with the proposed two-stage in vitro methodology seem to be adequate for the evaluation of dissolution in the lower intestine.

In Vivo Predictive Models for Oral Drug Absorption

Dr. Nikoletta Fotaki (University of Bath, UK) discussed the use of biorelevant *in vitro* data within a physiologically-based pharmacokinetic (PBPK) model environment for the

391 prediction of *in vivo* performance with a focus on the points to be considered and the
392 challenges regarding the type of *in vivo* predictive data needed. Due to the pharmacokinetic
393 reasons for attrition in drug development the need for *in vivo* predictive in vitro tests and
394 the increased use of absorption modeling during drug development are evident (37). The
395 first aspects discussed related to the methodology of *in vivo* predictive solubility and
396 dissolution studies in terms of 1) the appropriate medium to be used (buffers,
397 pharmacopoeia media, biorelevant media), 2) the continuous update of the biorelevant
398 media based on physiological data (i.e. FaSSIF V1/ V2/ V3) and 3) the type of *in vitro*
399 dissolution apparatus to be used (USP dissolution apparatus I-IV and other approaches such
400 as Dissolution Stress Test Device, TNO Intestinal Models). A case study in which a
401 successful IVIVC for an immediate and a prolonged release formulation of a BCS Class II
402 compound was achieved based on appropriate selection of *in vitro* conditions (media,
403 apparatus) in combination with PBPK modeling was presented. The impact of *in vitro*
404 hydrodynamics on the development of *in vitro-in vivo* correlations for modified release
405 formulations of a BCS Class II compound, were discussed in the second case study (38). It
406 was shown that the hydrodynamics of USP apparatus II, III and IV may all be adequate as a
407 starting point for generating IVIVCs of up to 7 mm monolithic dosage forms with low drug
408 load, at least in the fasted state. The next point discussed related to the need of appropriate
409 *in vivo* predictive enzyme and transporter data apart from the solubility/ dissolution data in
410 the PBPK models. The third case study involved the development of a successful IVIVC
411 for an amorphous sustained release formulation of a BCS Class II compound based on
412 appropriate selection of *in vitro* conditions (media, apparatus) and enzyme/transporter data

in combination with PBPK modeling. In the cases that the compound undergoes *in vivo* degradation, biorelevant *in vitro* degradation data has to be generated and used as an input in the PBPK model. This was revealed through the fourth case study in which the development of a successful IVIVC for an amorphous formulation of a BCS Class II compound based on appropriate selection of *in vitro* conditions (media, apparatus) and *in vitro* degradation data in combination with PBPK modeling was shown. In the last part of her presentation she elaborated on the characterization of the dissolution of other components of the formulation apart from the API, such as functional excipients or co-formers in co-crystals that can play a vital role in the assessment of bioavailability (39, 40)

Physiologically Based Pharmacokinetic Simulations Integrating In Vitro Dissolution Results for Preclinical and Clinical Formulation Development

Dr. Neil Parrott (F Hoffmann LaRoche) presented a pharmaceutical industry perspective on the utility of physiologically based absorption models integrating biorelevant *in vitro* dissolution data to guide formulation development. Within Roche, absorption modeling plays a key role in biopharmaceutics sub-teams which are formed to address formulation challenges in a project. The sub-teams bring together expertise in drug metabolism and pharmacokinetics, clinical pharmacology and formulation and the models provides an invaluable platform for integration of data, hypothesis generation and extrapolation. This is illustrated with 2 case studies. The first shows how an oral absorption model, developed in GastroPlus™, can be verified with Phase 1 data for immediate-release capsules and then applied to understand drug release from Phase 2 tablets and granules and to develop an in

vitro-in vivo correlation (IVIVC) model with biorelevant USP2 dissolution data and the mechanistic absorption model (41). The second example covers the application of physiologically based absorption modeling during the late stage clinical development and filing of Alectinib (42). The modelling helped to predict and understand the impact of food and gastric pH changes on Alectinib absorption.

The Impact of In Vivo Predictive Dissolution on Generic Drug Development and Review

Dr. Robert Lionberger (Food and Drug Administration, USA) presented that *in vivo* predictive dissolution (IVPD) could have its highest impact on generic drugs and be a path to expand access to generic competition. Many generic products are in small markets where the cost of an *in vivo* bioequivalence study could be a significant barrier to entry. This is an opportunity for IVPD to make a positive public health impact by supporting *efficient in vitro* bioequivalence standards. FDA has guidance that provides for BCS biowaivers for class 1 and 3 drug products, but BCS class 2 and 4 are where IVPD is the critical step. IVPD needs to be linked closely with modeling and simulation of drug absorption and distribution to fully characterize risks of bioavailability or bioequivalence differences. Between 2013 and 2017 under GDUFA I, FDA has support a wide variety of research to close some of the scientific gaps related to bioequivalence. As we move in to GDUFA II, it is time to move toward implementation of IVPD for generic drugs.

Future improvement and direction

In order to understand the bioperformance of the drug substance and product of interest, great progresses have been made in recent years. Scientists have been developing and

conducting science-centric researches to advance the area of *in vivo* prediction. Many scientists agreed that *in vivo* predictive dissolutions and computational approaches would be the right direction and the future to improve the oral drug dosage forms and to predict *in vivo* plasma profiles. The development of decision tree to select an appropriate dissolution methodology and experimental conditions for the test API formulation was extensively discussed to direct the formulation and analytical scientists and to harmonize the *in vitro* dissolution methodologies based on BCS and physicochemical properties. However, there is no clear answer for the selection of one methodology over the other methodologies. Thus, the different dissolution and simulation methodologies can be offered to scientists and regulatory agents as a toolbox and they can freely select the methodologies for their purposes.

Two important questions are: 1) if the scientific community can cross-validate their own experimental/computational methodologies and/or harmonize their experimental methodologies so that the results and agreements/disagreements could be discussed on the same ground, and 2) if the scientific community and the regulatory community can develop the field of new *in vitro* dissolution methodologies for bioequivalence and *in vivo* predictive dissolution and harmonize the common ground. Academia, industry and regulators should collaborate to derive the maximum benefit from *in vivo* predictive dissolution and computational applications. It would be mutual benefit to all to expand our knowledge and advance this area of sciences.

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References

1. Krieg BJ, Taghavi SM, Amidon GL, Amidon GE. In vivo predictive dissolution: transport analysis of the CO2 , bicarbonate in vivo buffer system. J Pharm Sci. 2014;103(11):3473-90.
2. Krieg BJ, Taghavi SM, Amidon GL, Amidon GE. In Vivo Predictive Dissolution: Comparing the Effect of Bicarbonate and Phosphate Buffer on the Dissolution of Weak Acids and Weak Bases. J Pharm Sci. 2015;104(9):2894-904.
3. Cristofoletti R, Dressman JB. FaSSIF-V3, but not compendial media, appropriately detects differences in the peak and extent of exposure between reference and test formulations of ibuprofen. Eur J Pharm Biopharm. 2016;105:134-40.
4. Cristofoletti R, Dressman JB. Matching phosphate and maleate buffer systems for dissolution of weak acids: Equivalence in terms of buffer capacity of bulk solution or surface pH? Eur J Pharm Biopharm. 2016;103:104-8.
5. Cristofoletti R, Dressman JB. Dissolution Methods to Increasing Discriminatory Power of In Vitro Dissolution Testing for Ibuprofen Free Acid and Its Salts. J Pharm Sci. 2017;106(1):92-9.
6. Litou C, Vertzoni M, Xu W, Kesisoglou F, Reppas C. The impact of reduced gastric acid secretion on dissolution of salts of weak bases in the fasted upper gastrointestinal lumen: Data in biorelevant media and in human aspirates. Eur J Pharm Biopharm. 2017;115:94-101.
7. Hens B, Tsume Y, Bermejo M, Paixao P, Koenigsknecht MJ, Baker JR, et al. Low Buffer Capacity and Alternating Motility along the Human Gastrointestinal Tract: Implications for in Vivo Dissolution and Absorption of Ionizable Drugs. Mol Pharm. 2017;14(12):4281-94.

8. Bergstrom CA, Holm R, Jorgensen SA, Andersson SB, Artursson P, Beato S, et al. Early pharmaceutical profiling to predict oral drug absorption: current status and unmet needs. Eur J Pharm Sci. 2014;57:173-99.
9. Riethorst D, Mols R, Duchateau G, Tack J, Brouwers J, Augustijns P. Characterization of Human Duodenal Fluids in Fasted and Fed State Conditions. J Pharm Sci. 2016;105(2):673-81.
10. Hasselbalch KA. Die Berechnung der Wasserstoffzahl des Blutes aus der freien und gebundenen Kohlensäure desselben, und die Sauerstoffbindung des Blutes als Funktion der Wasserstoffzahl. Biochemische Z. 1916;78:112-44.
11. Jain N, Yalkowsky SH. Estimation of the aqueous solubility I: application to organic nonelectrolytes. J Pharm Sci. 2001;90(2):234-52.
12. Bergstrom CAS, Charman WN, Porter CJH. Computational prediction of formulation strategies for beyond-rule-of-5 compounds. Adv Drug Deliv Rev. 2016;101:6-21.
13. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12(3):413-20.
14. Sugano K, Terada K. Rate- and Extent-Limiting Factors of Oral Drug Absorption: Theory and Applications. J Pharm Sci. 2015;104(9):2777-88.
15. Tsume Y, Mudie DM, Langguth P, Amidon GE, Amidon GL. The Biopharmaceutics Classification System: subclasses for in vivo predictive dissolution (IPD) methodology and IVIVC. Eur J Pharm Sci. 2014;57:152-63.
16. Stewart AM, Grass ME, Brodeur TJ, Goodwin AK, Morgen MM, Friesen DT, et al. Impact of Drug-Rich Colloids of Itraconazole and HPMCAS on Membrane Flux in Vitro and Oral Bioavailability in Rats. Mol Pharm. 2017;14(7):2437-49.
17. Stewart AM, Grass ME, Mudie DM, Morgen MM, Friesen DT, Vodak DT. Development of a Biorelevant, Material-Sparing Membrane Flux Test for Rapid Screening of Bioavailability-Enhancing Drug Product Formulations. Mol Pharm. 2017;14(6):2032-46.
18. Yu A, Baker JR, Fioritto AF, Wang Y, Luo R, Li S, et al. Measurement of in vivo Gastrointestinal Release and Dissolution of Three Locally Acting Mesalamine Formulations in Regions of the Human Gastrointestinal Tract. Mol Pharm. 2017;14(2):345-58.
19. Koenigsknecht MJ, Baker JR, Wen B, Frances A, Zhang H, Yu A, et al. In Vivo Dissolution and Systemic Absorption of Immediate Release Ibuprofen in Human Gastrointestinal Tract under Fed and Fasted Conditions. Mol Pharm. 2017;14(12):4295-304.
20. Mudie DM, Shi Y, Ping H, Gao P, Amidon GL, Amidon GE. Mechanistic analysis of solute transport in an in vitro physiological two-phase dissolution apparatus. Biopharm Drug Dispos. 2012;33(7):378-402.
21. Shi Y, Erickson B, Jayasankar A, Lu L, Marsh K, Menon R, et al. Assessing Supersaturation and Its Impact on In Vivo Bioavailability of a Low-Solubility Compound ABT-072 With a Dual pH, Two-Phase Dissolution Method. J Pharm Sci. 2016;105(9):2886-95.

22. Xu H, Vela S, Shi Y, Marroum P, Gao P. In Vitro Characterization of Ritonavir Drug Products and Correlation to Human in Vivo Performance. Mol Pharm. 2017;14(11):3801-14.
23. Xu H, Shi Y, Vela S, Marroum P, Gao P. Developing Quantitative In Vitro-In Vivo Correlation for Fenofibrate Immediate-Release Formulations With the Biphasic Dissolution-Partition Test Method. J Pharm Sci. 2017.
24. Tsume Y, Matsui K, Searls AL, Takeuchi S, Amidon GE, Sun D, et al. The impact of supersaturation level for oral absorption of BCS class IIb drugs, dipyridamole and ketoconazole, using in vivo predictive dissolution system: Gastrointestinal Simulator (GIS). Eur J Pharm Sci. 2017;102:126-39.
25. Tsume Y, Takeuchi S, Matsui K, Amidon GE, Amidon GL. In vitro dissolution methodology, mini-Gastrointestinal Simulator (mGIS), predicts better in vivo dissolution of a weak base drug, dasatinib. Eur J Pharm Sci. 2015;76:203-12.
26. Takeuchi S, Tsume Y, Amidon GE, Amidon GL. Evaluation of a three compartment in vitro gastrointestinal simulator dissolution apparatus to predict in vivo dissolution. J Pharm Sci. 2014;103(11):3416-22.
27. Matsui K, Tsume Y, Amidon GE, Amidon GL. In Vitro Dissolution of Fluconazole and Dipyridamole in Gastrointestinal Simulator (GIS), Predicting in Vivo Dissolution and Drug-Drug Interaction Caused by Acid-Reducing Agents. Mol Pharm. 2015;12(7):2418-28.
28. Matsui K, Tsume Y, Amidon GE, Amidon GL. The Evaluation of In Vitro Drug Dissolution of Commercially Available Oral Dosage Forms for Itraconazole in Gastrointestinal Simulator With Biorelevant Media. J Pharm Sci. 2016;105(9):2804-14.
29. Matsui K, Tsume Y, Takeuchi S, Searls A, Amidon GL. Utilization of Gastrointestinal Simulator, an in Vivo Predictive Dissolution Methodology, Coupled with Computational Approach To Forecast Oral Absorption of Dipyridamole. Mol Pharm. 2017;14(4):1181-9.
30. Tsume Y, Langguth P, Garcia-Arieta A, Amidon GL. In silico prediction of drug dissolution and absorption with variation in intestinal pH for BCS class II weak acid drugs: ibuprofen and ketoprofen. Biopharm Drug Dispos. 2012;33(7):366-77.
31. Tsume Y, Igawa N, Drelich AJ, Amidon GE, Amidon GL. The Combination of GIS and Biphasic to Better Predict In Vivo Dissolution of BCS Class IIb Drugs, Ketoconazole and Raloxifene. J Pharm Sci. 2017.
32. Reppas C, Karatza E, Goumas C, Markopoulos C, Vertzoni M. Characterization of Contents of Distal Ileum and Cecum to Which Drugs/Drug Products are Exposed During Bioavailability/Bioequivalence Studies in Healthy Adults. Pharm Res. 2015;32(10):3338-49.
33. Diakidou A, Vertzoni M, Goumas K, Soderlind E, Abrahamsson B, Dressman J, et al. Characterization of the contents of ascending colon to which drugs are exposed after oral administration to healthy adults. Pharm Res. 2009;26(9):2141-51.
34. Markopoulos C, Vertzoni M, Symillides M, Kesisoglou F, Reppas C. Two-Stage Single-Compartment Models to Evaluate Dissolution in the Lower Intestine. J Pharm Sci. 2015;104(9):2986-97.

35. Markopoulos C, Andreas CJ, Vertzoni M, Dressman J, Reppas C. In-vitro simulation of luminal conditions for evaluation of performance of oral drug products: Choosing the appropriate test media. Eur J Pharm Biopharm. 2015;93:173-82.
36. Georgaka D, Butler J, Kesisoglou F, Reppas C, Vertzoni M. Evaluation of Dissolution in the Lower Intestine and Its Impact on the Absorption Process of High Dose Low Solubility Drugs. Mol Pharm. 2017;14(12):4181-91.
37. Fotaki N. Pros and cons of methods used for the prediction of oral drug absorption. Expert Rev Clin Pharmacol. 2009;2(2):195-208.
38. Fotaki N, Aivaliotis A, Butler J, Dressman J, Fischbach M, Hempenstall J, et al. A comparative study of different release apparatus in generating in vitro-in vivo correlations for extended release formulations. Eur J Pharm Biopharm. 2009;73(1):115-20.
39. Bittner B, McIntyre C, Tian H, Tang K, Shah N, Phuapradit W, et al. Phase I clinical study to select a novel oral formulation for ibandronate containing the excipient sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC). Pharmazie. 2012;67(3):233-41.
40. Tomaszewska I, Karki S, Shur J, Price R, Fotaki N. Pharmaceutical characterisation and evaluation of cocrystals: Importance of in vitro dissolution conditions and type of coformer. Int J Pharm. 2013;453(2):380-8.
41. Stillhart C, Parrott NJ, Lindenberg M, Chalus P, Bentley D, Szepes A. Characterising Drug Release from Immediate-Release Formulations of a Poorly Soluble Compound, Basmisanil, Through Absorption Modelling and Dissolution Testing. AAPS J. 2017;19(3):827-36.
42. Parrott NJ, Yu LJ, Takano R, Nakamura M, Morcos PN. Physiologically Based Absorption Modeling to Explore the Impact of Food and Gastric pH Changes on the Pharmacokinetics of Alectinib. AAPS J. 2016;18(6):1464-74.