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1 ***In vivo* predictive dissolution and simulation workshop report: Facilitating the**  
2 **development of oral drug formulation and the prediction of oral bioperformance**  
3  
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35

36 **Abstract**

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

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

## 59 **Introduction**

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

72 The objectives of this workshop were to:

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

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

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

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

112

### 113 **Day 1**

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

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

122 dissolution media that yields a surface pH ( $\text{pH}_0$ ) representative of *in vivo* conditions (1-6).  
123 The improved understanding of bicarbonate as a buffer is important and confirms that  
124 luminal bicarbonate buffer concentration and buffer capacity is very low and this is  
125 critically important to developing methodologies that reflect *in vivo*  $\text{pH}_0$  (7). This more  
126 comprehensive understanding of *in vivo* hydrodynamic and chemical conditions will allow  
127 for physiologically and physicochemically relevant *in vitro* dissolution testing to be  
128 performed on a sound, scientific basis.

### 129 **In Vivo Gastrointestinal Fluid Composition and Effects of Drug Substance**

#### 130 **Physicochemical Properties on Solubilization**

131 Dr. Christel Bergström (Uppsala University) continued with a thorough presentation of  
132 composition of human intestinal fluids. She emphasized that recent clinical studies pointed  
133 at a higher pH in the stomach than that typically used in compendial media (median of 2.5  
134 with a range of 1.7-3.3 in comparison to compendial pH of 1.0-1.2), a lower buffer capacity  
135 in the upper gastrointestinal tract than previously thought, and a larger intra- and inter-  
136 individual variability in bile salts and phospholipids than previously has been reported (7-  
137 9). These factors may significantly affect both dissolution rate and solubilization in the  
138 human intestinal tract. For this reason, there is not a single biorelevant medium that can be  
139 used to provide insights into the expected variability of dissolution rate and solubilization;  
140 rather a number of biorelevant media is likely to be needed to provide insights into the  
141 expected variability *in vivo*. She then linked the performance of drugs to their  
142 physicochemical properties and in particular pointed at the usefulness of understanding the  
143 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

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

187 **Dissolution Methodologies and Selection of Study Conditions Based upon Drug**

188 **Physicochemical Characteristics (BCS subclass) & Dosage Forms**

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

205 **Direct Measurement of In Vivo Dissolution of IR and MR Drug Products in Human**

206 **GI Tract**

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

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

231 **Interpreting Drug Concentration Profiles in Plasma and Relating Them to In Vitro**

232 **Dissolution Measurements/In Silico Predictions**

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

250

251 ***iPD Methodologies – Future***

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

266

## 267 **Day 2**

### 268 **A Two-Phase Dissolution-Partition Test for Characterizing BCS II Drugs Products** 269 **and Establishing IVIVR**

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

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

286

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

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

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

302

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

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



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

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

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

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

346

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

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

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

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

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

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

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

### 388 ***In Vivo Predictive Models for Oral Drug Absorption***

389 Dr. Nikoletta Fotaki (University of Bath, UK) discussed the use of biorelevant *in vitro* data  
390 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

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

422

### 423 ***Physiologically Based Pharmacokinetic Simulations Integrating In Vitro Dissolution***

#### 424 ***Results for Preclinical and Clinical Formulation Development***

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

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

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

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

453

#### 454 **Future improvement and direction**

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

457 conducting science-centric researches to advance the area of *in vivo* prediction. Many  
458 scientists agreed that *in vivo* predictive dissolutions and computational approaches would  
459 be the right direction and the future to improve the oral drug dosage forms and to predict *in*  
460 *vivo* plasma profiles. The development of decision tree to select an appropriate dissolution  
461 methodology and experimental conditions for the test API formulation was extensively  
462 discussed to direct the formulation and analytical scientists and to harmonize the *in vitro*  
463 dissolution methodologies based on BCS and physicochemical properties. However, there  
464 is no clear answer for the selection of one methodology over the other methodologies.  
465 Thus, the different dissolution and simulation methodologies can be offered to scientists  
466 and regulatory agents as a toolbox and they can freely select the methodologies for their  
467 purposes.  
468 Two important questions are: 1) if the scientific community can cross-validate their own  
469 experimental/computational methodologies and/or harmonize their experimental  
470 methodologies so that the results and agreements/disagreements could be discussed on the  
471 same ground, and 2) if the scientific community and the regulatory community can develop  
472 the field of new *in vitro* dissolution methodologies for bioequivalence and *in vivo*  
473 predictive dissolution and harmonize the common ground. Academia, industry and  
474 regulators should collaborate to derive the maximum benefit from *in vivo* predictive  
475 dissolution and computational applications. It would be mutual benefit to all to expand our  
476 knowledge and advance this area of sciences.

477

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