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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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33 **Keywords:** *in vivo* prediction, formulation prediction, simulation, dissolution

34

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 (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* 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[®]), 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 GastroplusTM 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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