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# Establishing the Bioequivalence Safe Space for Immediate-Release Oral Dosage Forms using Physiologically Based Biopharmaceutics Modeling (PBBM): Case Studies

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ABSTRACT

For oral drug products, *in vitro* dissolution is the most used surrogate of in vivo dissolution and absorption. In the context of drug product quality, safe space is defined as the boundaries of in vitro dissolution, and relevant quality attributes, within which drug product variants are expected to be bioequivalent to each other. It would be highly desirable if the safe space could be established via a direct link between available in vitro data and in vivo pharmacokinetics. In response to the challenges with establishing in vitro-in vivo correlations (IVIVC) with traditional modeling approaches, physiologically based biopharmaceutics modeling (PBBM) has been gaining increased attention. In this manuscript we report five case studies on using PBBM to establish a safe space for BCS Class 2 and 4 across different companies, including applications in an industrial setting for both internal decision making or regulatory applications. The case studies provide an opportunity to reflect on practical vs. ideal datasets for safe space development, the methodologies for incorporating dissolution data in the model and the criteria used for model validation and application. PBBM and safe space, still represent an evolving field and more examples are needed to drive development of best practices.



## Introduction

Consistent clinical performance is paramount to the successful commercialization of drug products, while understanding of the link between drug product quality and performance is at the center of Quality by Design (QbD). In practice, consistent clinical performance of commercial drug products is ensured by appropriate design space(s) and control strategies including drug substance and drug product specifications (e.g., in vitro dissolution testing, solid state, particle size), and is further supported by relevant clinical data, such as relative bioavailability and bioequivalence (BE) studies. Specifically, chemistry, manufacturing and controls (CMC) changes that are likely to have an impact on the drug product's in vitro performance and ultimately the patient, necessitate in vivo studies or a biowaiver request supported with the appropriate data.

Under the context of drug product quality and biopharmaceutics, the concept of safe space, defined by boundaries of in vitro dissolution and/or other relevant quality attributes, such as active pharmaceutical ingredient (API) particle size, within which drug product variants are anticipated to be bioequivalent to one another,[1–5] offers an integrated approach to biowaivers which could expand beyond the regulatory framework established around Biopharmaceutics

*Abbreviations:* API, Active Pharmaceutical Ingredient; BCS, Biopharmaceutics Classification System; BE, Bioequivalence; IR, Immediate Release; IVIVC, In Vitro-In Vivo Correlation; MR, Modified Release; PBBM, Physiologically Based Biopharmaceutics Modeling; MAM, Mechanistic Absorption Modeling; PBPK, Physiologically Based Pharmacokinetics; PK, Pharmacokinetics; PSD, Particle Size Distribution; PE, Prediction Error.

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Classification System (BCS) and in-vitro-in-vivo correlations (IVIVC). A safe space can be established via conventional (e.g., bracketing approach) and modeling (both conventional and mechanistic) approaches, with dissolution testing most commonly used as in vitro surrogate of the in vivo performance. In the case of bracketing approach, where safe space is established directly based on the results of a relative bioavailability study when formulation/process variants exhibiting different in vitro dissolution profiles are shown to be bioequivalent, the relationship between dissolution and in vivo absorption, although acceptable for regulatory decision making, is a qualitative one. Therefore, extrapolation of the safe space to formulation/process variants beyond those tested in the clinical study, i.e., the knowledge space, is currently not a recommended practice from regulatory perspective. Thus, it would be highly desirable if the safe space concept could be supported and expanded via establishment of a direct link between the available in vitro data and in vivo pharmacokinetics.

For BCS 1 and 3 compounds formulated as immediate release (IR) dosage forms, the BCS biowaiver framework provides a straightforward approach to the establishment of a safe space. As long as the guidance recommendations are met including the prescribed dissolution criteria for rapid (BCS 1) and very rapid (BCS 3) dissolution, the safe space is considered self-evident. In those cases, the establishment of a safe space relying on available in vitro and pharmacokinetic (PK) data offers the opportunity to expand the BCS 1/3 regulatory framework (e.g., obtain wider dissolution acceptance criterion). For BCS 2 and 4 compounds formulated as IR and for all modified release (MR) drug products, the link between dissolution and in vivo performance (i.e., PK) has been traditionally accomplished via the establishment of conventional, non-mechanistic IVIVCs. The different levels of IVIVC and recommendations for their development, validation and applications are well defined in available regulatory guidances.[6,7]

Despite the well-established framework, success rates for IVIVCs generally remain low, especially for IR products.[3] In practice, establishment of IVIVCs, although considered the gold standard approach to biowaivers, is hampered both by inherent compound and formulation properties as well as lack of biopredictive dissolution methods.[8] In response to the challenges with establishing traditional IVIVCs, physiologically based biopharmaceutics modeling (PBBM) has been gaining increased attention to help establish the essential in vitro – in vivo link and to build a safe space,[2–5,8,9] as also evident by the recent draft US FDA guidance on physiologically based pharmacokinetics (PBPK) modeling for biopharmaceutics applications.[1] This modeling approach to safe space has the advantage of not being confined to building an IVIVC, hence increasing the likelihood of gaining regulatory flexibility. PBBM allows for a mechanistic understanding of the *in vivo* drug release and its interaction with the physiology resulting in in vitro/ in vivo relationships (IVIVRs) and offering a potential alternate path to biowaivers, especially for IR products. However, since safe space establishment via PBBM and its regulatory application represents an evolving field, best practices for model development are still developing and more examples of model applications are needed.[2–5,8,9]

In this article, we describe real case studies collected across pharmaceutical companies which offer the opportunity to further reflect on the use of PBBM for establishing a safe space for IR formulations of BCS Class 2 and 4 compounds. The case studies demonstrate successful application of different methodologies for incorporation of observed or modeled dissolution data informed by drug and product specific considerations. Several statistical methods and criteria to establish the safe space from point estimates analogous to the existing IVIVC guidance and virtual BE tools, are also discussed. Finally, we list challenges and make recommendations to further advance the use of modeling to build safe space, including suitable model validation steps and model applications.

## Case Studies

### *General Considerations and Modeling Approaches*

All simulations were conducted using GastroPlus® software v.9.0 –v.9.7 (Simulations Plus, Inc. Lancaster, CA). Physicochemical and pharmacokinetic input parameters for all case studies are summarized in Table 1 while the detailed input parameter information is provided in the Supplementary Material. All models used the default Opt logD model SA/V 6.1 ASF model setting. Dissolution data input was either as is (case studies 1 and 5) or using the z-factor model (case studies 2–4). Additional details on dissolution data models are discussed within each case study as appropriate. Here the term model validation is used to refer to the entire model evaluation process (including not fit-for-purpose applications) to qualify the model to inform decision making.[10]

### *Case study 1: Retrospective Modeling-Based Assessment of BE Safe Space for Vandetanib Tablets*

#### *Compound Physicochemical and Biopharmaceutics Properties*

Vandetanib is a weak base with *Log D* 4.7 (pH 11) and pKa 5.2 (for the aminoquinazoline moiety) and 9.4 (for the piperidine moiety). Vandetanib has high permeability and is highly soluble in acidic media. At pH greater than 6 the solubility is low. Upon oral administration, Tmax occurs between 4 and 7.5 h. Following once daily administration of a solution formulation, the PK are linear over the range of 100–600 mg and absorption is > 90%.[11,12]

Dickinson et al.[11] previously reported in vitro dissolution profiles for vandetanib formulation variants, Variant A (standard tablet), Variant B (larger particle size), Variant C (process variant) and Variant D (formulation variant) in several media of pH 1.2, pH 4.5, pH 6.8 and water with surfactant. All formulations were shown to be bioequivalent in vivo.[11,13] There are no known non-bioequivalent formulation of vandetanib. The BE safe space for different variants of vandetanib tablets was established clinically and as such the PBBM was applied to provide insight into in vivo dissolution/absorption characteristics of the drug.

#### *Simulation Methodology*

The developed model was first verified[10] by comparing the simulated PK profiles with those observed for the oral solution[11] as well as for the 300 mg oral dose from vandetanib PK interaction study with rifampicin reported by Martin et al.[14] (see Supplementary Material). In vitro dissolution data generated at pH 1.2 representing the acidic stomach environment, showed the greatest discrimination between Variant A (standard tablet) and Variant D (formulation variant), and were used as dissolution input as they represented the extremes of the tested dissolution space. Simulations for vandetanib tablet Variant A and Variant D were conducted by incorporating the corresponding in vitro dissolution profiles generated at pH 1.2 (see Supplementary Material) into the model. The in vivo dissolution, absorption, and compartmental absorption profiles for Variant A and Variant D were compared to establish a safe space.

#### *Results and Discussion*

The dissolution and the absorption profiles of the two variants, obtained via PBBM, are overlaid in Figure 1. As evidenced from the overlaid in vivo absorption profiles of Variant A and Variant D, the absorption is gradual showing marginal initial differences between the two variants. At about 2 h, the profiles are practically overlapping. The compartmental absorption data shown in the Supplementary

**Table 1**
Key Input Parameters for Simulations for Case Studies 1-5.

| Parameter | Vandetanib | Etoricoxib | Dasatinib | JNJ-X | NOV-Z |
|---|---|---|---|---|---|
| Molecular weight (g/mol) | 475.4 | 358.9 | 488.01 | N/A | N/A |
| Log P | 4.7 | 2.28 (log D, pH 7.0) | 1.8 | ~3 | >3 |
| pKa | 5.2 (b); 9.4 (b) | 4.5 (b) | 5.334 (b) | Neutral | ~4 (b), ~6 (b) |
| pH – solubility profile (mg/mL) | 0.1M HCl: 41<br>pH 3: 6.4<br>pH 7: 0.3 | pH 2.0: 25.1<br>pH 3.07: 2.01<br>pH 3.54: 0.7<br>pH 4.01: 0.3<br>pH 4.54: 0.14<br>pH 5.03: 0.09<br>pH 5.47: 0.08<br>pH 6.8 = 0.073 | pH 2.6: 18<br>pH 4.0: 0.036<br>pH 6.0: 0.0063<br>pH 6.5: 0.0068 | Intrinsic: 0.04<br>FaSSIF: 0.55<br>FeSSIF: 5.04 | 0.1M HCl: 0.1<br>pH6.8: 0.0<br>FaSSIF: 0.1 |
| Effective human permeability (cm/s) | $1.354 \times 10^{-4}$ | $4.48 \times 10^{-4}$ | $2.5 \times 10^{-4}$ | $1.85 \times 10^{-4}$ | $1.7 \times 10^{-4}$ |
| Precipitation time (s) | 900 | 10000 | 1300 | 900 | 3600 |
| Dissolution model | Dissolution data input as CR: Dispersed | z-factor<br>IR Tablet | z-factor<br>IR tablet | z-factor<br>IR tablet | Weibull function, Dissolution data input as CR:Dispersed |
| Dissolution data | pH 1.2 | Multiple pH 2, 6.8, single dose, 120 mg | pH 4.0 Acetate buffer containing 1% Triton X-100 | Biorelevant | QC method |
| Surface pH correction | N/A | pH 2 dissolution profiles only | No (modest effect expected at pH 4) | N/A | N/A |
| Interpolation | N/A | Fasted release to slower release | 100 mg to new lower 20 mg dose | Development of a new formulation | PBBM to supersede failed F2 |
| Disposition Data | Oral Solution | IV | Oral Solution | IV | Wajima Method |
| Disposition model parameters | Vc/F = 27 L/kg<br>CL/F = 12 L/hr<br>K12 = 0.003 1/hr<br>K21 = 0.006 1/hr | Vc = 35.49 L<br>CL = 3.19 L/hr<br>K12 = 0.62 1/hr<br>K21 = 0.28 1/hr<br>FPE = 0% | Vc = 2.69 L/kg<br>CL = 61.5 L/hr | CL = 0.142 L/hr/kg<br>Vc = 0.15 L/kg<br>K12 = 2.561/hr<br>K21 = 0.63 1/hr<br>K13 = 0.63 1/hr<br>K31 = 0.084 1/hr<br>FPE liver = 12% | CL = 0.4 L/h/kg,<br>Vc = 1.4 L/kg<br>K12 = 0.16 1/h,<br>K21 = 0.05 1/h,<br>FPE Liver = 25% |

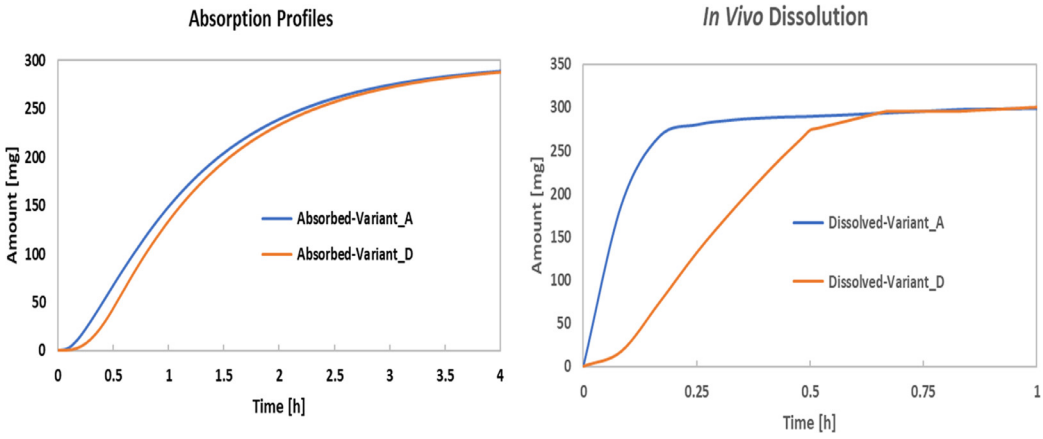


**Figure 1.** Case study 1 - Overlay of absorption (left panel) in vivo dissolution profiles (right panel) of Variant A and Variant D. Gastrointestinal regional absorption for both variants is shown in Fig. S2.

material also suggest very similar absorption pattern for the two variants (Figure S2). For the two extremes, represented by Variant A (standard tablet) and Variant D (formulation variant), as the in vivo absorption rates are significantly slower than dissolution rates, absorption is practically unaffected by dissolution differences as long as a complete release is achieved within 30 min. Therefore, for a drug with gradual absorption and a late Tmax, the dissolution differences at early time points (i.e., up to 30 min in vandetanib case) are considered irrelevant and not biopredictive for the in vivo performance. The in vitro dissolution differences at early time points are shown to somewhat impact extent of gastrointestinal regional absorption (i.e., 19.5% vs 14.4% absorbed in duodenum and 17.1% vs 19.4% in jejunum 1 from Variant A and Variant D, respectively) without affecting the overall extent of absorption (i.e., 99.9% from both variants) and in vivo performance (Figure S2).

*Case study 2: Safe Space Determination for Etoricoxib Tablets*

*Compound Physicochemical and Biopharmaceutics Properties*

Etoricoxib is a weak base with pKa 4.5 and high solubility in stomach pH (25 mg/mL in 0.01N HCl) and much lower solubility (~0.07 mg/mL) at pH 6.8. The free base is used in the clinical formulation. Bioavailability is 100% in the normal fasted state and the compound exhibits linear pharmacokinetics.[15]

A PBBM model for etoricoxib was previously reported[16] and adopted for the work presented in this manuscript with modifications to reflect additional dissolution data. The intent of the original model was to inform probability of success for executing a BE study for two batches from different manufacturing sites. The model is focused on the highest dose of 120 mg used in reported BE studies.[16] To visualize the model validation, data from a clinical study which included a cross-over IV and PO administration were used.[17]

*Simulation Methodology*

The modeling strategy was to describe the baseline pharmacokinetic data for etoricoxib reference tablets (original manufacturing site) and extrapolate the dissolution space via simulations to understand the BE bounds. Dissolution data for the reference tablets were available at pH 2 and pH 6.8. Due to the weak base nature of the API, surface pH needs to be taken into account in simulating dissolution data in acidic media following the approach suggested by Pepin et al.[18] Disintegration of etoricoxib tablets is fast and thus was not taken into account for the modeling. Dissolution data were modeled in two steps. In the first step, data at pH 6.8 were fitted to the z-factor model. At pH 6.8 etoricoxib is unionized and the impact of surface pH is negligible, thus surface pH correction was considered unnecessary. The z-factor was then subsequently varied in stepwise fashion to define the safe space at pH 6.8 until the simulated Cmax was at least 20% lower. In the second step, pH 2.0 media dissolution data were modeled. The surface pH at bulk pH 2.0 was calculated to be 2.85, which was then used in the z-factor approach. The z-factor was then again varied in a stepwise function to capture the dissolution data and model the safe space. All simulations of dissolution experiments were conducted in the GastroPlus® software by setting the stomach pH and volume to the pH and volume of the media of interest or the surface pH and increasing the stomach transit time to maintain a constant volume during the simulation as previously suggested.[16]

*Results and Discussion*

At pH 6.8 dissolution of etoricoxib is slow due to the suboptimal solubility and a z-factor value of $3 \times 10^{-3}$ mL/mg/s adequately described the dissolution data as shown in Figure 2. To match the

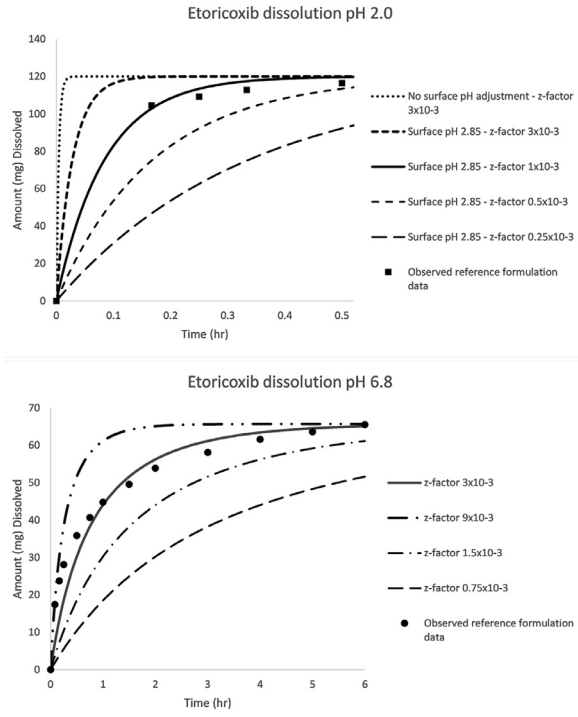


**Figure 2.** Case Study 2 - Z-factor estimates for etoricoxib dissolution at pH 2.0 (top) and pH 6.8 (bottom) (USP 2, 50 rpm).

**Table 2**
Estimation of Safe Space for Etoricoxib 120 Mg Tablets (Estimated Pharmacokinetic Parameters).

| Stomach (pH 2) z-factor mL/mg/s | Intestinal (pH 6.8) z-factor mL/mg/s | $C_{max}$ ng/mL | AUC ng*h/mL | Min/Max $C_{max}$ | Min/Max AUC |
|---|---|---|---|---|---|
| 3 × 10-3 | 9 × 10-3 | 1.81 | 35.8 | - | - |
| 1 × 10-3 | 3 × 10-3 | 1.73 | 35.8 | 95.6% | 100% |
| 0.5 × 10-3 | 1.5 × 10-3 | 1.63 | 35.6 | 90.0% | 99.4% |
| 0.25 × 10-3 | 0.75 × 10-3 | 1.45 | 34.7 | 80.1% | 96.9% |

observed dissolution data at pH 2.0 a z-factor of $1 \times 10^{-3}$ mL/mg/s was estimated (Figure 2). This small difference in z-factor may represent either somewhat different dissolution kinetics at different pH values or a misspecification of the approximated surface pH which may be affected by buffer species and other formulation excipients (a surface pH of 3.3 which is only a small difference from 2.85 results in z-factor of $3 \times 10^{-3}$ mL/mg/s). For the purposes of further simulations, the z-factor of $1 \times 10^{-3}$ mL/mg/s was adopted as the baseline for dissolution in the stomach and the pH 6.8 z-factor was adopted for all intestinal compartments.

The developed model accurately described the observed pharmacokinetic data for etoricoxib (see Supplementary Material for plasma concentration profile). The prediction errors are 8.5% for Cmax and 10% for AUC0-120 h, well within typically acceptable error ranges. The model predicts 99.8% bioavailability in line with the clinical data.[15] To establish the safe space, simulations were run by adjusting the z-factor values in the stomach and intestinal compartments (for the purposes of this manuscript any adjustment was proportional in both compartments). A difference less than 20% between maximal and minimal AUC or Cmax was considered to denote a safe space following the principles of the IVIVC guidance. The simulations outcome is summarized in Table 2 and the corresponding dissolution profiles are included in Figure 2. AUC was in this case, largely insensitive to dissolution changes. Due to the high solubility in the acidic stomach pH, etoricoxib practically behaves like a BCS 1 compound, and as long as the rapid dissolution criteria as defined by BCS are met, formulations are expected to be similar even for Cmax. As the intent of this analysis was to broadly assess the safe space for etoricoxib dissolution, virtual BE simulations were not conducted. To the best of our knowledge, previous modeling reports focused on single medium dissolution input and here we propose that the concept of safe space could be expanded to multimedia dissolution data in some cases.

### *Case study 3: Establishment of Safe Space to Support a Biowaiver for Lower Strength Dasatinib Tablets*

#### *Compound Physicochemical and Biopharmaceutics Properties*

Dasatinib is a weak base with Log P of 1.8[19] and pKa of 5.3. It is a crystalline white powder. The solubility is high at acidic condition (18 mg/mL at pH 2.6) and as pH increases, the solubility decreases drastically to 0.006 mg/mL at pH 6. After oral administration, the Cmax was between 0.5 and 6 h and dasatinib exhibits dose proportional increase in AUC and linear elimination characteristics over the dose range of 15–240 mg/day.[20] Pharmacokinetic parameters were derived from the published literature.[21]

A fully replicate BE study was conducted at 100mg strength in healthy human subjects and a waiver was applied for 20mg strength based on comparative dissolution in QC media (pH 4.0 Acetate buffer containing 1% Triton X-100). Despite similarity testing meeting regulatory standards (f2=59) between 100mg and 20mg in QC media, the release of 20mg was found to be rapid (87% in 30 min) whereas for the higher 100mg strength the dissolution was found to be not rapid (78% in 30 min). A regulatory agency denied the biowaiver for the lower 20mg strength due to differences in dissolution in QC media between the 20mg and 100mg strength. The agency had asked to conduct a BE study for 20mg strength for marketing authorization of the lower strength. In order to justify that the differences between dissolution profiles between the two strengths do not alter in vivo performance, PBBM modeling was utilized, as described in this case study. Based on this PBBM modeling approach, a biowaiver was granted for lower strength 20mg by a regulatory agency and the BE study was avoided.

#### *Simulation Methodology*

The modeling strategy included utilizing pH solubility profile obtained from the literature and the pKa [19]. The standard particle size (D50 of 25 $\mu$m) was used for both test and reference formulations in this case study. The permeability and mean precipitation time were fitted to obtain the observed data. The blood to plasma ratio and plasma protein binding were obtained from the literature. Due to absence of intravenous (i.v.) data for dasatinib, the literature obtained clearance and volume of distribution, corrected against the bioavailability fraction were used. The difference in the dissolution profiles were incorporated in the model using z-factor approach for both strengths 100 and 20mg as indicated in Figure 3 (raw data provided in Supplementary material). The model validation was performed against simulation outcome for pivotal 100mg reference and test formulations.

#### *Results and Discussion*

Model predictions are shown in Figure 4. Prediction errors for Cmax, AUC0-inf and AUC0-t were 2.6%, 7.7%, and 2.9% for the test product and 4.5%, 14.0%, and 0.6% for the reference formulation. Hence the model was considered validated.

As a next step, the rapid dissolution profile of 20mg batch was considered as a worst case for the 100mg strength and was fitted using Z-factor and used for the simulation for the 100mg strength. The results of all the simulations are provided in Table 3. As shown in Table 3, the test to reference (T/R) ratio's between predicted and observed 100mg pivotal test [B/A from Table 3] were within the BE limits. Using the faster dissolution profile of the 20mg strength for the 100mg strength resulted in equivalent pharmacokinetic parameters as that of the pivotal test 100mg drug product. The T/R ratio's [C/B from Table 3] between 100mg predicted using 20mg dissolution profile and 100mg predicted using 100mg dissolution profiles were also within the BE limits of 0.8 -1.25. Hence, the faster dissolution profile of the 20mg strength did not lead to differences in BE under in vivo conditions due to dissolution differences. The application of PBBM in this specific case study is considered of low risk given that the strengths are proportionally similar in composition, f2>50, PK is linear within this range and the manufacturing process and mechanism of release are the same for both strengths. Low impact PBBM models along with totality of data may justify the creation of a safe space based on simulations rather than knowledge space (i.e., observed in vitro dissolution with corresponding PK profiles).

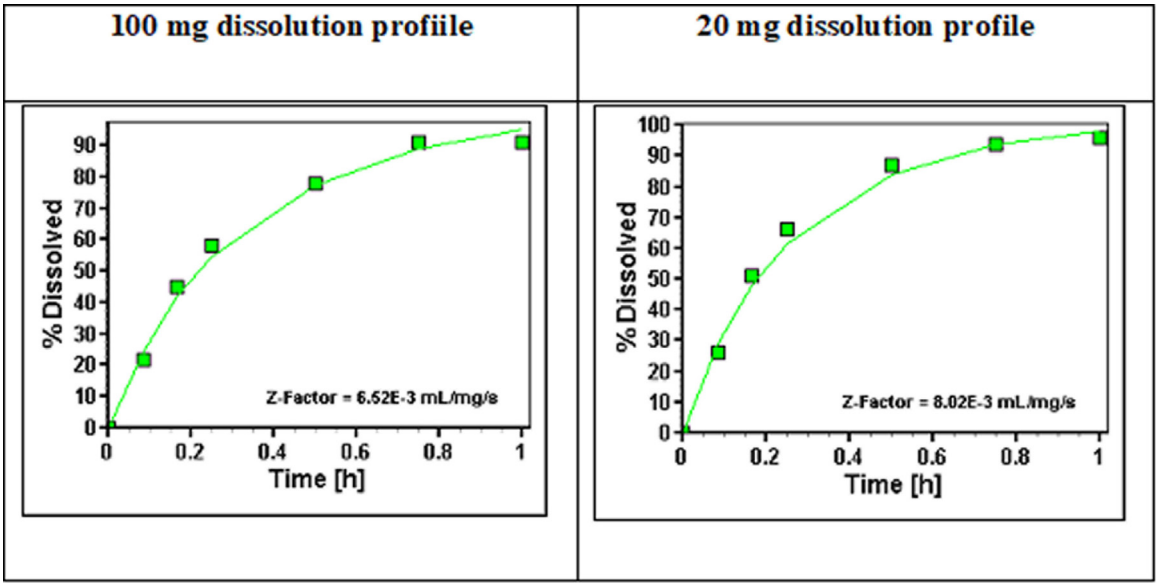


**Figure 3.** Case Study 3 - Dissolution profiles of dasatinib 100mg and 20mg test products along with Z-factor fitting (pH 4.0 Acetate buffer containing 1% Triton X-100, USP 2)

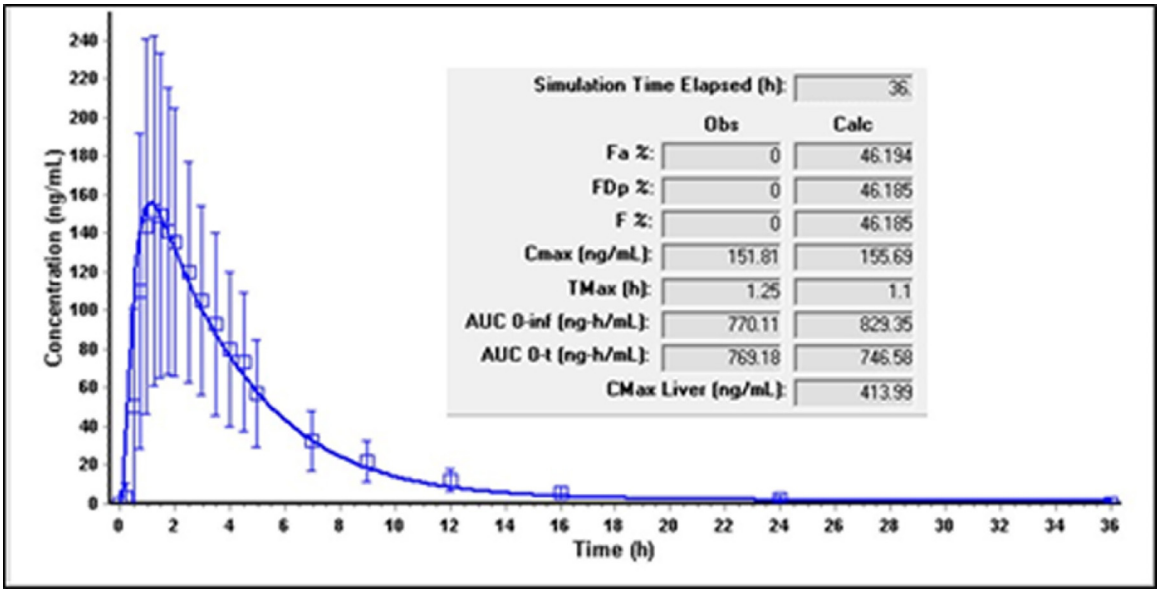


**Figure 4.** Case Study 3 - The Gastroplus simulation outcome for pivotal 100mg test product (utilizing 100mg dissolution profile with z-factor input). The reference product is shown in Fig. S5.

**Table 3**
Comparison of Observed and Predicted Dasatinib Pharmacokinetic Parameters Utilizing Various Dissolution Profiles as Input.

| PK Parameter | $T_{max}$ (h) | $C_{max}$ (ng/mL) | $AUC_{0\text{-}inf}$ (ng.h/mL) | $AUC_{0\text{-}t}$ (ng.h/mL) |
|---|---|---|---|---|
| Observed mean values from 100mg pivotal test [A] | 1.25 | 151.81 | 770.11 | 769.18 |
| Predicted using 100 mg pivotal test dissolution input [B] | 1.1 | 155.69 | 829.35 | 746.58 |
| Predicted for 100 mg using 20mg dissolution input [C] | 1.1 | 155.93 | 840.44 | 752.28 |
| T/R Ratio [B/A] | N.A. | 102.56 | 107.69 | 97.06 |
| T/R Ratio [C/B] | N.A. | 100.15 | 101.34 | 100.76 |

*Case study 4: Establishment of a Safe Space for A BCS Class 4 Compound in a Novel Fixed Dose Combination Tablet*

*Compound Physicochemical and Biopharmaceutics Properties*

JNJ-X is an orally administered non-ionizable compound with Log P about 3, low solubility (intrinsic solubility 0.04 mg/mL) and moderate permeability. After oral administration Tmax generally occurs between 1 and 2 h. JNJ-X was formulated in several immediate release drug products, either as a single agent or in a fixed dose combination tablet. For the latter, the co-administered compounds were dosed as their respective specialty formulations during phase 3 development of the pursued clinical indication. In parallel, a novel combination tablet was developed that allows patients to reduce the pill burden to a single formulation. The compound is practically insoluble in water, irrespective of pH, but undergoes substantial solubilization in the presence of bile. A tenfold increased solubility and intrinsic dissolution rate was observed comparing the biorelevant intestinal media in fasted and fed state. The absence of any in vivo effect of a high-fat meal on the absorption of JNJ-X however indicates that such differences in solubility will likely not affect the intestinal absorption.

In a first risk assessment the potential impact of the API particle size specifications based on a biorelevant dissolution study and a PBBM model was investigated. Later, an in silico bridging approach on polymorphic purity was performed by applying the same biorelevant dissolution based PBBM model approach. The modeling outcome was subjected to a confirmatory clinical study validating the outcome of the in vitro and in silico biopharmaceutical risk assessment. For earlier work, the reader is referred to McAllister M et al.[22]

The quality control (QC) dissolution method developed for the drug product was demonstrated to have sufficient discriminatory capabilities, including the API particle size. However, setting and justification of the dissolution specification based on solely the pivotal batches was at risk of rejecting tablet batches manufactured with drug substance batches at the boundaries of the API particle size distribution of the production process (Figure 5). The intent of the PBBM was to establish a safe space to demonstrate that the API particle size specifications and the corresponding proposed dissolution criterion are adequate to ensure consistent drug product performance compared to that of the pivotal clinical batches.

*Simulation Methodology*

The pH solubility profile was fitted from the available in vitro measurements. Bile salt solubilization was implemented by calculating the solubilization ratio from FaSSIF and FeSSIF in vitro solubility. Observed differences in the dissolution rate related to formulation properties, API particle size and polymorphism were incorporated in the model using the z-factor approach. It was opted not to use the API particle size-based models as these are unable to pick up the potential formulation effects between different drug products. Potential formulation variables of the combination tablet were bridged by applying the same biorelevant dissolution methodology to the different drug products. The method was designed to simulate physiologic gastro−intestinal conditions in human adults and includes a transition phase of the gastric to the intestinal environment conditions similarly to the two-stage protocol as recently described by the OrBiTo consortium.[23]

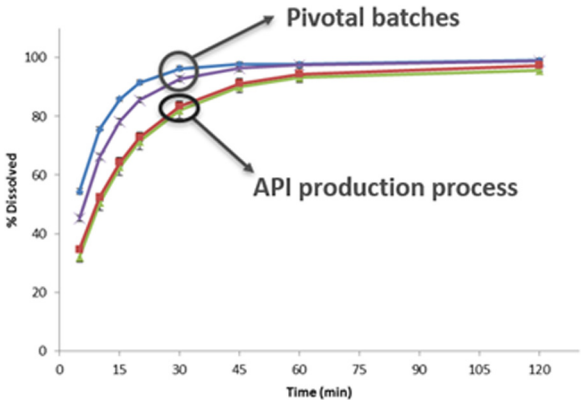


**Figure 5.** Case Study 4 - Average QC dissolution profiles of JNJ-X commercial scale batches produced with drug substance of different particle sizes. The error bars represent the standard deviation.

*Results and Discussion*

Biorelevant dissolution profiles with corresponding clinical data of different formulations with different particle sizes and polymorphic content were considered for the development and validation of the PBBM approach. Crossover virtual bioequivalence (VBE) trials were performed based on intestinal variability parameters and in vivo PK characteristics. The VBE trials were designed to simulate the respective clinical study protocols with respect to sample size, dose administration, drug product and nutritional state. An example of the VBE outcome is illustrated in Figure 6 for the reference batch of theBE study. The corresponding BE statistics of test and reference formulations in vivo and in silico (including intra-subject variability) is provided in Supplementary Material.

In a next step, the PBBM model and the biorelevant dissolution profiles of the drug products with different API particle sizes were used to assess the potential impact of the QC dissolution profiles, and by inference the API particle size, on the oral bioavailability of the compound with the purpose to understand the dimensions of the safe space given narrow safe space obtained using the observed dissolution and clinical data. Based on a parameter sensitivity analysis and VBE assessment, the in vitro dissolution profiles did not indicate significant risks within the ranges evaluated. Significant changes in the dissolution rate, well beyond the observed range from the biorelevant dissolution results are required to result in clinically relevant changes in exposure compared to the in vivo results of the pivotal batches. These findings are illustrated in ($C_{max}$ only) visualizing the required change in biorelevant dissolution profile to obtain a 10% difference in exposure with the pivotal batch (Figure 7).

*Case study 5: PBBM to Support a Biowaiver for a Manufacturing Site Change of a BCS Class 4 Compound*

*Compound Physicochemical and Biopharmaceutics Properties*

NVS-Z is a salt of a weak base (pKa ~4 and 6) and is characterized as a lipophilic drug (logP>3) with low aqueous solubility and low/moderate permeability and is an IR formulation. Solubility in 0.1N HCl is ~0.1 mg/mL while at pH 6.8, the compound is nearly insoluble. Bile salts increase the solubility slightly (Table 1). After oral administration average Tmax is approximately 4 h (Figure 8). To support a manufacturing site transfer and minor process adaptations, a comparative dissolution study of pre- and post-change batches was performed under 4 different dissolution conditions in the physiological pH range of 1 to 6.8 including the dissolution QC method, which contained surfactant. The dissolution study resulted in the observation that f2 similarity failed for some, with batch-to-batch variability within the pre-change batches.

*Simulation Methodology*

To evaluate whether the failed f2 similarity tests were of in vivo relevance, a PBBM investigation using GastroPlus® was performed. In the absence of i.v. data, preclinical PK parameters such as clearance (CL) and volume of distribution (Vss) were utilized to predict the human CL and Vss using allometric scaling methods. The inter-

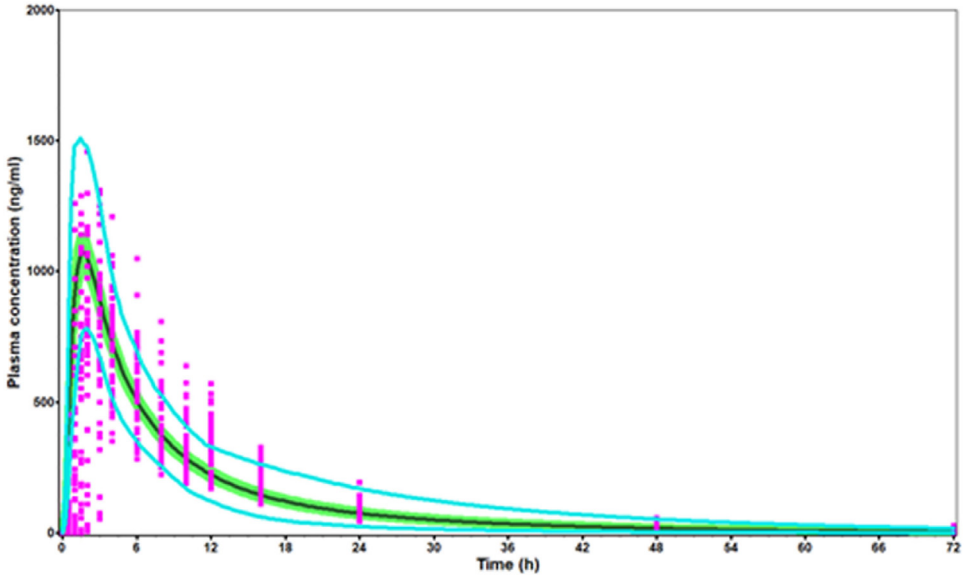


**Figure 6.** Case Study 4 - PBBM predicted (green – – –) concentration–time profile with the 95% probability plots (blue – – –) of JNJ-X. The comparison is made with the observed (□) concentration–time profiles.

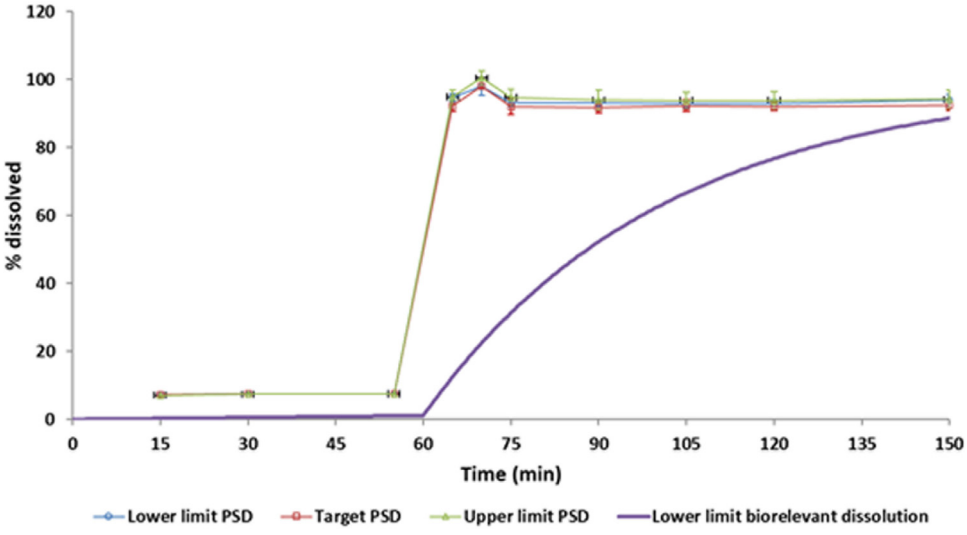


**Figure 7.** Case Study 4 - Estimation of dissolution safe space (as related to Cmax) for JNJ-X.

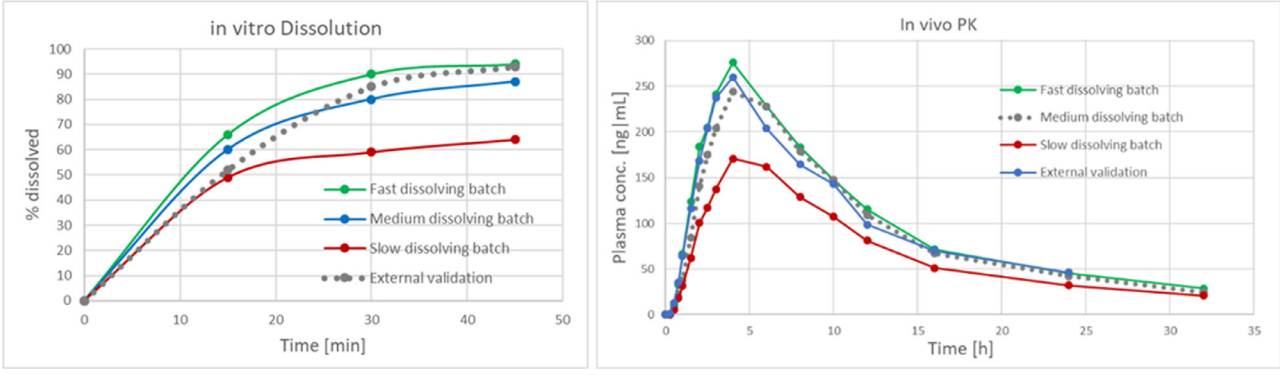


**Figure 8.** Case Study 5 - NVS-Z in vivo and in vitro profiles. The red in vivo PK curve is non-BE to the fast and medium releasing batches and corresponds to the slow release batch in red

compartment distribution rate constant (k12, k21) was obtained by using 2-compartment model PK analysis of human i.v. PK profile generated with the Wajima method. The QC dissolution profiles fitted by a Weibull function were used as input parameters in the CR-mode. The model was set up based on a BE study in which 3 formulations were clinically tested with fast, medium and slow dissolution characteristics. The slow dissolving variant was not bioequivalent to the fast dissolving batch, which was the reference batch. The medium dissolving batch demonstrated BE to the fast dissolving batch. The plasma concentration profiles and the related dissolution profiles are shown in Figure 8.

*Results and Discussion*

The PBPK model showed an acceptable prediction (Supplemental Figure S6). The individual prediction errors (PE%) for the fast and medium dissolving batches were in the range of 2–7% for both the AUCinf and Cmax, whereas the slow dissolving batch returned 17% and 22%, respectively. While the PK of the slow dissolving non-BE batch was slightly overpredicted, this batch was correctly predicted by PBBM to be non-bioequivalent to the fast dissolving batch. The QC method and specification are consistent with the outcome of the BE study and the simulations as the slow dissolving batch did not pass the dissolution acceptance criterion. Next, the model was externally validated with the outcome of another BA study with acceptable prediction errors for AUCinf and Cmax of 12% and 0%, respectively. The mean PE% for all four batches were 10 and 8%, respectively. Parameter sensitivity analyses demonstrated that the precipitation time and the bile salt solubilization were the most important parameters which impact the absorption and bioavailability. The PBBM could show that the non-BE batch was adequately discriminated by the model. A BE safe space was set up in that the dissolution profile of the medium dissolving batch is considered to be the lower boundary of a dissolution safe space. All batches with faster dissolution were considered to be bioequivalent. The latter assumption was confirmed by BA studies using suspensions with a very rapid dissolution, which demonstrated slightly higher, but still similar PK parameters compared with the fast dissolving tablet batch. This PBBM model was applied to the transfer batches, which exhibited dissolution profiles within the dissolution safe space, and the simulation results demonstrated that the non-similar dissolution characteristics among the transfer batches obtained in the comparative dissolution study does not remarkably affect the absorption and systemic exposure in humans. The transfer batches were simulated to be bioequivalent to each other and also to the fast releasing batch used in the BE study as reference. An extended approach is described in the supplementary section, which shows AUC and Cmax safe space (Figure S7).

## Discussion

Recent workshops[24] have described three approaches that can be used to establish a safe space, with significant potential and impact towards expedited drug development.

1. Qualitative relationship between in vitro dissolution and clinical exposure – this approach entails conducting relative bioavailability study(s) using formulations with different dissolution profiles. If the formulations meet BE criteria, then the clinically relevant specifications will be based on the dissolution profile of the slowest dissolving batch.
2. Conventional IVIVCs[6]
3. Oral PBPK models for biopharmaceutic applications (or PBBM)[5,24]

In this manuscript we provide examples of the latter application, detailing five case studies from the pharmaceutical industry (Table 1, Table 4). From a regulatory viewpoint, safe space applications have

**Table 4**
Summary for Predictive Performance of BE Safe Space.

| Case Study | Data for Model Validation | Decision Consequence, Model Impact (Kuemmel[29]) | Criteria for Model Validation of Predicted Parameters | Safe Space Estimation Approach | Model Application |
|---|---|---|---|---|---|
| Case 1, Vandetanib | Data from 4 formulation variants (including target formulation) from cross over study. Disposition parameters were obtained from oral solution data | Low, Retrospective Analysis | PE % [A, B] for $C_{max}$, AUC | ≤15% population mean = high confidence | Retrospective analysis, not submitted to HA(s) |
| Case 2, Etoricoxib | Dissolution data from pH 2, pH 6.8 (USP 2, 50 rpm). Mean i.v. data were used for disposition parameters | Moderate – high. Safe Space for Manufacturing | PE % [A, B] for $C_{max}$, AUC < 10% | Max-min = 20% | Internal Decision Making |
| Case 3, Dasatinib | Dissolution data from pH 4. Two dose strength were used. Mean i.v. data were used for disposition parameters | Moderate, Biowaiver for lower strength | PE % [A, B] for $C_{max}$, AUC < 15% | ≤20% population mean = high confidence T/R < 20% | Submitted to HA(s) |
| Case 4, JNJ-X | Biorelevant dissolution data of different formulations, different strengths, and different API particle sizes. Mean i.v. data were used for disposition parameters | Moderate to high. API particle size specification and quality control dissolution safe space | PE % [A, B] for $C_{max}$, AUC | ≤20% population mean = high confidence Geometric mean ratio, T/R (90% CI) < 20% | Submitted to HA(s) |
| Case 5, NVS-Z | QC Method Dissolution data from 3 formulation variants from cross over study and from one additional study for external validation. | High, Biowaiver for Site Transfer Batches | PE % [A, B] < 10 % for $C_{max}$, AUC for fast and moderate release, < 25% for slow release non-BE. | PBBM demonstrated BE for transfer batches within 0.8 to 1.25 range for site transfer badges. PBBM superseded failed f2. | Submitted to HA(s) |

A: Prediction error for mean: PE%=|(predicted - observed)/(observed)| × 100
B: A maximal difference of 20% in the predicted Cmax and AUC from the PBPK model can be accepted (in line with IVIVC guidance[6]).”

the potential for acceptance by global regulatory agencies, provided the PBBM is built and validated appropriately.[10,23] Safe space applications in drug product quality have significant PBBM refinement and validation requirements, which have been described in the 2020 released draft guidance from US FDA on use of PBPK in biopharmaceutic applications for oral drug products.[1] For example, to increase confidence in PBBM, it is "*strongly recommend that sponsors demonstrate the model's predictive performance based on PK data from batches exhibiting unacceptable BA*", i.e. the inclusion of non-bioequivalent batches with matching non-BE clinical data is recommended.

Safe space applications in drug product development are diverse. The industry case studies presented in here show possibilities for establishing a safe space for immediate release formulations of BCS Class 2 and 4 compounds, with varying clinical data availability or safe space use. Among the presented models some supported regulatory applications while others were used for internal decision making (Table 4). Impacts include: a) successful BE assessments for company internal decision making (case 2); b) approved biowaivers for manufacturing site transfers submitted to global health authorities (case 5), c) retrospective analyses to guide formulation development (case 1); d) support of biowaivers for a new dose strength (case 3) or, e) the justification of API particle size specifications (case 4).

Development of PBBM necessitates the inclusion of drug parameters such as API physicochemical, formulation and PK data, as well as physiological parameters as described in detail in several publications.[2,4,5,18,24–26] In generating knowledge to support the definition of the safe space, it is important to rely on high quality dissolution and clinical data that can enable model validation and use. For the establishment of a safe-space via PBBM, specifically, clinical PK data with corresponding dissolution profiles from different formulation variants are generally needed to build the model. As part of model development and validation, a critical assessment of input parameters is important.

Given the endpoint of the safe space simulation is a "bioequivalent" dissolution profile, selection of the input methodology for dissolution data is probably the most critical decision at start of model development. As discussed in recent workshops,[24,25,27] while fully mechanistic dissolution models for all dosage forms are not readily available, it is generally preferred to use semi-mechanistic models over empirical models. For 3 out the 5 case studies reported in this manuscript, a semi-mechanistic model (z-factor) was indeed employed. In the case of etoricoxib an additional step was undertaken to incorporate the surface pH in the model to better simulate the in vitro dissolution data in acidic environment (pH 2) as previously suggested by Pepin et al.[18] However empirical models such as Weibull function may still represent an alternative option as long as the model is appropriately validated against appropriate datasets. For example in case study 5 the input dissolution data are shown to correctly predict a non-BE batch. In our experience, semi-mechanistic models are more useful for translation of dissolution data between different dissolution conditions (e.g. between multimedia datasets or between QC and biorelevant media) or when clinical validation datasets are more limited (e.g. non-BE batch is not available). Additional PBBM examples with successful semi-mechanistic (such as z-factor or p-psd) or empirical methods to model dissolution data and define the safe space can be found in the literature.[9,18,25,26]

For weak bases specifically, the precipitation kinetics is another important input for the simulation. It is generally acknowledged that prediction of in vivo precipitation from in vitro data is challenging. In our experience if precipitation is not seen in vitro, it is unlikely to be an issue in vivo and can be removed from the simulation as was done with case study 2. However, more commonly than not, precipitation kinetics need to be estimated following a top-down optimization approach as was the case with other case studies. The impact of the precipitation settings on the simulation can be also explored as part of parameter sensitivity analysis during model validation.

Common limitations/shortcomings for successful PBBM validation and application have been discussed in literature and recent workshops.[3,28] The two most common ones are: a) Lack of sufficient in vivo study data to build and validate the PBPK model; e.g. data on a single formulation variant are available or i.v. data are not available to define the disposition parameters and b) the dissolution methods chosen are not appropriate. Some of the case studies did not necessarily meet all desired guidance recommendations, such as inclusion of non-BE data. In our experience, it is commonly not feasible to manufacture non-BE batches. However that doesn't preclude appropriate model validation. For several of the case studies additional validation across clinical studies was performed (some of these are included in the Supplementary Material). In some cases this validation may not be necessary or is considered self-evident. E.g. for etoricoxib where bioavailability is 100%, simulation of additional studies would not provide substantially different information over simulating the well-controlled i.v./PO dataset. Similarly the lack of i.v. data can be addressed by the use of oral solution data for estimating the disposition parameters, as was done in case study 1 and 3.

Model validation acceptance criteria may be established prior to start of model building depending on the intended use of the model i.e., fit for purpose. Depending on the data used to build the model and robustness of model validation, the regulatory application could be impacted. Figure 9 shows schematically how single or multiple pH dissolution data from the reference batch (blue) can be linked to clinical outcomes by varying z-factor (slope) to alter the dissolution profiles (orange and grey) and to set up the safe space with BE pharmacokinetic profiles lower bound (orange) and non-BE (grey).

As per the 2020 draft guidance,[1] to evaluate whether a dissolution method is biopredictive, the predicted systemic exposure should be comparable (± 10%) to the observed in vivo PK data, if a cross-over study is used. For model validation, 10% PE may be a suitable criterion with PBBM in case data are available from controlled cross-over clinical study. In many safe-space PBBM applications, the PK profile is predicted across various independent studies based on average parameters for clearance, distribution, and permeability, among others. This makes it difficult to meet 10% cross study prediction error requirements. However, when independent clinical studies are included for model validation to demonstrate biopredictivity, a maximal difference of 20% in the predicted $C_{max}$ and AUC as estimated by a PBPK model could be acceptable, or predictive errors could fall in the 0.8–1.25 fold range, depending on whether decision impacts are low, moderate or high as described by Kuemmel et. al.[29] This was indeed the case for case study 5 where $C_{max}$ was over-predicted for a non-BE batch and PE was < 25% (Figure S6, right panel). This PE of > 10% was successfully justified, by demonstrating that this non-BE batch fell outside of the in vitro QC method criteria, thus not impacting clinical batches. In some cases health authorities have considered weight of evidence, or totality of evidence approaches in the model validation and acceptance for granting biowaivers[30] or in other non-oral PBPK model acceptances.[10]

In summary, cross industry experiences in PBBM applications for establishing a safe space for immediate release formulations of BCS Class 2 and 4 compounds have been described. This work highlights the importance of PBBM in mechanistically linking in vitro dissolution to clinical exposure for safe space generation to support the establishment of clinically relevant drug product specifications, scale-up and post-approval (SUPAC) activities (e.g. change in manufacturing site), biowaiver of lower strength and/or in development of fixed-dose combination products, etc., and adds to the

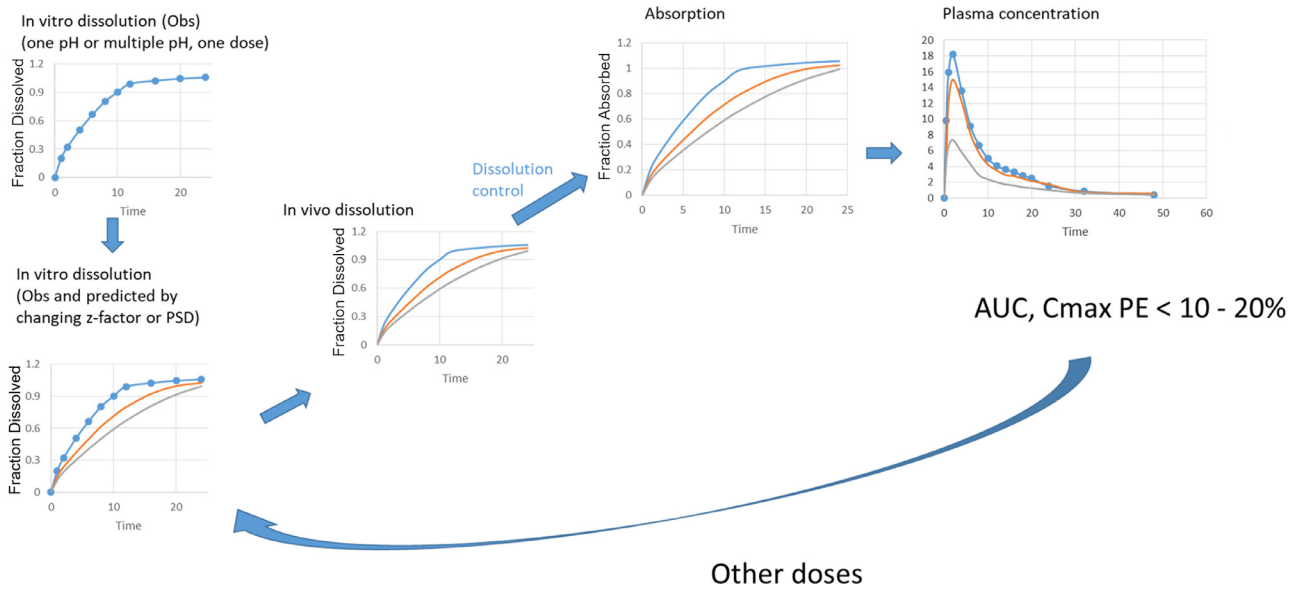


**Figure 9.** Schematic showing the safe space or BE space between blue and orange dissolution profiles.

growing literature in the field that is needed to increase confidence in this approach.

## Supplementary Materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.xphs.2021.09.017.

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