Review Article

Theme: Facilitating Oral Product Development and Reducing Regulatory Burden through Novel Approaches to Assess Bioavailability/Bioequivalence
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Effective Absorption Modeling in Relative Bioavailability Study Risk Assessment

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Abstract. Absorption modeling is an excellent strategic fit to perform a risk assessment for relative bioavailability (RBA) studies as it provides direct input into the question that is at the core of the RBA decision, namely, how does the absorption of the test drug product compare to the reference and is it likely to be different enough to justify an RBA study. The main limitation to absorption modeling in risk assessment is the inherent uncertainty associated with modeling. The extent to which the absorption modeling is integrated into the risk assessment should depend on the level of confidence in the modeling. It is difficult, however, to quantify the level of confidence on a case by case basis. The effective application of absorption modeling for RBA risk assessment therefore requires a general understanding of when modeling is expected to be reliable and also how to build reliability directly into the modeling. This paper describes a framework for effective modeling in RBA risk assessment that is based on four fundamental building blocks: (1) relate severity of drug product change and API properties to reliability of modeling, (2) use critical model variables to express the critical differences in the drug products, (3) generate a fraction-absorbed response surface expressed in terms of the critical model variables to evaluate the relative performance of the drug products, and (4) tie the first three building blocks together by following good model building practices that assure the highest quality model is built. The building blocks are demonstrated by a simple but common example of a change in solid state from free base to HCl salt.

KEY WORDS: absorption modeling; drug product; RBA study; relative bioavailability study; risk assessment.

INTRODUCTION

A human clinical study is a major undertaking and any work that can be done to reduce the number of studies can have a significant impact on the cost and efficiency of drug development. Relative bioavailability (RBA) studies represent one area where a reduction in clinical studies can be achieved. In the early phases of drug development, an RBA study is not a strict regulatory requirement, although there are certain situations when an RBA study is always a smart choice, such as controlled release or enabled formulations. For a majority of cases, the drug product change is exposure neutral and an RBA study can be avoided, or at least minimized, without any real impact on the clinical path. Many of these RBA studies are still conducted simply because of a prevailing zero-risk attitude, basically that it is always too risky to omit an RBA study. RBA risk assessment

could help to break this pattern by providing a rational understanding of the overall risk associated with not doing an RBA study. Absorption modeling is an important factor that should be incorporated into the RBA risk assessment. Other factors are prior preclinical and clinical *in vivo* data, pharmacokinetic behavior, biopharmaceutics properties, clinical development phase, type of drug product change, and *in vitro* dissolution data.

The decision about how to incorporate dissolution data into the risk assessment is a critical one. In theory, if an *in vitro*–*in vivo* correlation exists, dissolution data can be used to project the relative *in vivo* performance of drug products. One approach is to incorporate dissolution results directly into the risk assessment as an independent factor. Indeed, in some RBA risk assessment frameworks the RBA decision is based solely on dissolution data. The BCS classification system (1) is an example of this type of framework where biowavers are granted based on dissolution data for class I compounds. Dissolution results can also be incorporated into the risk assessment indirectly as input into the absorption modeling. One interesting approach for capturing dissolution data in absorption modeling was described by Gao *et al.* (2). A limitation associated with dissolution data that must be recognized is that the drug material is often not available for

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testing at the time that the RBA decision must be made. To avoid this limitation, in this paper, we focus on the role of absorption modeling in RBA risk assessment independent of any dissolution data.

A risk assessment generally consists of two components, impact and probability. For an RBA risk assessment, the impact component represents the consequences of not doing an RBA study, *i.e.*, lost information about any necessary dose adjustments. The probability component represents the probability that the test drug product(s) will not satisfy the RBA criteria. For RBA studies, the impact component is a function of the phase of clinical development, sensitivity of exposure to dose, safety information, and finally the projected efficacy exposure requirements based on biomarkers or preclinical predictions. Absorption is a key factor in the second component, and in fact, for cases where the pharmacokinetics are linear, absorption is the only factor that determines the relative *in vivo* performance of the drug products. The goal of absorption modeling in RBA risk assessment is to provide a virtual assessment of the relative absorption of the drug products.

A significant limitation associated with absorption modeling that must be acknowledged, and in general this applies to any kind of computer modeling, is the lack of a general quantitative method for estimating confidence levels (3) associated with predictions. It is possible to some degree to use statistical measures of accuracy derived from cross-validation or retrospective studies, such as R^2 or RMSE, to assess the general reliability of individual predictions, but strictly speaking, these measures are relevant only in situations where a large number of predictions is performed. For this reason, it is extremely important to build reliability into the modeling in a “reliability by design” approach that is similar to quality by design. Towards this goal, this paper discusses a set of building blocks for effective absorption modeling in RBA risk assessment which is designed to make the absorption modeling as reliable as possible within a given situation. If modeling is applied in RBA situations where it has the potential to be accurate, and these building blocks are followed, then the modeling can be utilized as an important component in an RBA risk assessment.

BUILDING BLOCKS FOR EFFECTIVE ABSORPTION MODELING IN RBA RISK ASSESSMENT

Absorption modeling is in many ways the ideal tool for RBA risk assessment. It is the best way to leverage all of the data, *in vitro* and *in vivo*, in a holistic way to evaluate the relative performance of the drug products. The absorption modeling yields a virtual assessment that provides the exact information needed to make the RBA decision, that is, the predicted relative performance of the drug products in terms of fraction absorbed (Fa), or other pharmacokinetic endpoints, such as area under curve (AUC), Cmax, or Tmax. Although the strategic fit of absorption modeling is excellent, the impact of the modeling ultimately depends on how much confidence is placed in the modeling, and based on this confidence, to what extent the modeling is incorporated into the RBA decision. Commercial programs such as GastroPlus® have made it extremely facile to take a set of data and build an absorption model that appears to be “good,” but with this ease

of use comes a greater risk of generating misleading results. Ideally, there would be a way to mathematically quantify the confidence level of the predictions and use this objectively measure as the means for assigning a level of importance to the predictions. Since no such generally applicable method for doing this exists, our approach to this problem is to rely on empirical observations about when absorption modeling is expected to deliver reliable predictions and focus on key building blocks that are designed to build reliability directly into the modeling. The four building blocks in this scheme being: (1) drug product complexity, (2) critical model variables, (3) RBA Fa response surface, and (4) good model building practices. The fourth building block is not independent of the other the first three and is really a way of tying them together.

Relation of Severity of Drug Product Change and API Properties to Model Reliability

A critical question for any risk assessment is the importance level assigned to each factor or variable that figures into the risk calculation, and this is especially true for the absorption modeling predictions, where the importance level should be correlated with the confidence in the predictions. If the confidence is high, then in principle, the modeling is all you would need to make the RBA decision. If confidence in the predictions is low, then the importance level assigned to them should correspondingly be low. Reality is typically between these extremes and the challenge becomes finding a way to assign a confidence level to the modeling. With no quantitative mathematical method for doing this, options are limited. One way is to use a phenomenological approach and relate the reliability of the modeling to the following broad properties of the active pharmaceutical ingredient (API) and drug product: (1) complexity of the general absorption behavior of the API, (2) complexity of the test drug product, *i.e.*, drug in capsule *vs.* tablet, and (3) severity of drug product change, that is, how different is the test drug product from the reference. The complexity of the reference drug product is also important but not as important as the test drug product because there is prior clinical data for the reference drug product. The basic premise of this approach is that as the sensitivity to the absorption variables or the number of variables or factors that could impact absorption increases, the reliability of the absorption modeling decreases. Consider how the three factors listed above impact the reliability of the modeling. First, as the complexity of the general absorption behavior of the API increases, for example active uptake or highly variable precipitation, it becomes more sensitive to slight changes in the drug product, thus decreasing confidence in the modeling. Second, as the complexity of the test drug product increases, even for API with simple, straightforward absorption behavior, the number of factors that could potentially impact absorption, positively or negative, increases. Lastly, as the severity of the drug product changes, the test drug product becomes a wider extrapolation from reference drug product absorption model, thereby increasing the chances that critical variables will be omitted. This approach is analogous to the SUPAC guidelines (4) for formulation changes. Table 1 attempts to summarize the complexity and estimate the corresponding reliability level associated with some common drug product changes.

Critical Model Variables

Critical model variables are a simple idea but have major implications in regards to how absorption modeling for RBA risk assessment is performed and also interpreted. Critical model variables are the variables in the model used to express or represent the critical property and attribute differences between the two drug products. The properties are deemed critical because they have the potential to bring about a difference in the *in vivo* performance between the drug products. Properties that are different but would not cause any difference in the *in vivo* performance, *i.e.*, an inert excipient, would not be considered a critical property. The critical model variables are the variables that absolutely must be incorporated into a model if it is going to be able to accurately describe the relative *in vivo* performance of the two drug products. In mathematical terms, they are the variables that any differences in absorption depend most strongly on, *i.e.*, $\Delta Fa / \Delta X_{cmv}$, where ΔFa is the difference in fraction absorbed between the two drug products, X_{cmv} is a critical model variable, and ΔX_{cmv} represents the difference in the critical model variable for the two drug products. Critical model variables are basically an extension of the critical quality attributes concept.

A simple example of the critical model variable idea is the case of two drug products that are identical except for the API particle size distributions. In this example, any differences in absorption must ultimately be due to the particle size differences, and therefore, the critical model variables would be those variables that are used to represent the particle size distribution. Another example would be a change from drug in capsule to formulated drug in capsule where the API is identical for the two drug products. In this example, all important the interactions between the API and excipients in the formulated capsule must be considered in terms of how they could impact absorption. Identifying all of the important interactions related to the API and excipients, even when they are not obvious, and expressing them with the most fundamental variables so that they can be built into a model in a general way, is the main challenge to absorption modeling. Surprising results for RBA studies are often explained in terms of some variable or interaction that was assumed to not be important.

Applying the concept of critical model variables improves reliability of the modeling by placing emphasis on building a model that can be used to directly compare the two drug products. It results in a model that not only can be used to predict the quantitative differences in absorption but also to describe the underlying causes of the differences. In the context of RBA risk assessment, it is not enough to simply predict *Fa* for the drug products. It is important to also understand the variables that cause the differences and know their relative quantitative impact. In more common terms, critical model variables essentially frame the modeling in terms of a parameter sensitivity analysis, which greatly simplifies interpretation. The critical model variables are also the variables that define the *Fa* response surface (next section).

How are the critical model variables identified? The process or method by which the critical model variables are selected is obviously crucial and is admittedly the limiting

factor in the whole approach. It is best to identify the critical model variables at the most fundamental level, but this will be strictly limited by the mathematical framework of the model. If the framework is simple and high level, then the variables will be as well, but as a result, the variables will be relatively easy to identify. If the framework is more complex, with many detailed interactions, then there is greater opportunity to assign the variables at a lower level, but this correspondingly makes identification more difficult. In the end, the process is one of hypothesis generation with confirmation by *in vitro* tests when possible. A common example would be *in vitro* testing of precipitation rates of API mixed with different excipients.

RBA *Fa* Response Surface

Applying the critical model variables approach essentially equates to building one overarching absorption model that is designed to relate the drug products. This means that one fraction-absorbed response surface can be generated that contains both drug products. The surface is expressed in terms of the critical model variables and the exact location of each drug product on the surface is determined by the values for the critical model variables. Figure 1 depicts an example of a typical response surface.

The *Fa* response surface is a graphical representation of the relationship between the critical model variables and fraction absorbed. The surface provides both the local and global information that is necessary to assess both the relative performance of the two drug products and also provide insight about the reliability of the predictions. Local information refers to the sensitivity of *Fa* to the critical model variables in the immediate vicinity of a drug product. Global information refers to the overall topology of the surface and how this ultimately determines the relative *Fa* of the drug products. Experience has shown that the more sensitive the surface, the less reliable the predictions. When there are more than two critical model variables, it is necessary to either generate projections of the full surface into three dimensions or limit the calculation to the two main variables that have the largest influence on absorption. Generating the response surface requires performing a large number of simulations, but this additional work is offset by the enhancement in interpretability.

Good Model Building Practices

The starting point for absorption modeling for RBA risk assessment is building an absorption model for the reference drug product. The reference model is built from the prior clinical data but must be built with consideration to link it up with the test drug product. Depending on the type of drug product change, there may be variables that are not important to the reference drug product but are critically important to the test drug product. Omitting these variables may not affect the results for the reference drug product, but the errors in the model are propagated through to the test drug product where they can lead to bad predictions. In some cases, the reliability of the modeling may be limited by the complexity of API/drug product, but it is still nonetheless always important to follow good model building practices to assure that for a given data package the best possible model is built. The following are meant as simple guiding principles for

Fig. 1. Example of an RBA Fa response surface. The surface reveals the relative position of the drug products and provides critical information about sensitivity of the surface around the drug product

good model building that have been accumulated over years of absorption modeling.

1. Use all available data to build model and do not just ignore inconsistencies in the data as measurement error; for example, *in vitro* data suggest high permeability and *in vivo* indicate low permeability. Critical insight can often be gained by reconciling inconsistencies in the data. This is frequently encountered between preclinical and clinical *in vivo* data.
2. Build absorption models from the ground up. Start by building preliminary models that employ both the *in vitro* and preclinical data. Use these models as the starting point for building more advanced models from the clinical data.
3. Minimize the number of variables optimized in the model. Do not just change a variable because it is the easiest way to fit the data.
4. Optimize the drug product variables before adjusting the physiological variables. It is often easy to fit data by adjusting

the physiological variables such as transit times or pH, but if the changes in the physiological variables are not physically justified, then error could be carried over into the drug product variables such as dissolution or permeability. Errors in the drug product variables make the model much less generalizable than errors in the physiological variables.

5. Pay close attention to how the pharmacokinetic (PK) parameters interplay with the absorption variables. Be aware of how errors in the PK parameters could propagate to errors in the absorption variables. Put more emphasis on fitting the absorption phase of the oral profile as compared to the elimination phase. Whenever possible, use the least complex PK model that fits the data.
6. Whenever possible, validate the final model, *e.g.*, build a model on the lowest clinical dose and test with all higher doses.

Two other corollaries to these general rules that are especially important for RBA risk assessment are:

1. Explicitly incorporate variability in physiological variables. Complexity enters when *in vivo* performance is strongly influenced by dose dependence and interaction of drug product with physiological conditions—mechanical properties, fed/fasted states, stomach transit, colonic transit time...
2. Focus on critical model variables. Try to make sure that best estimates are made for critical model variables for the reference drug product because these variables will make the connection with the test drug product.

EXAMPLE

This section describes an example of a drug product change where the reference formulation consists of a free base drug in capsule and the test formulation is a dry blend of an HCl salt in capsule. The dry blend ingredients are assumed to be inert and to not directly impact solubility or dissolution, and therefore, the critical difference in the drug products, *i.e.*, a difference that could impact absorption, is the solid state form of the API. Based on Table I, this type of drug product change would have a severity

Table I. Common Drug Product Changes in Early Drug Product Development

Type of change	Severity of change	Relationship to modeling
Polymorph	Simple	Polymorph changes in general have minor impact on solubility. Modeling should provide reliable estimate of RBA risk. One caution is impact of morphology on dissolution rate
API particle size	Simple	If particle size is only changed, modeling should be able to provide reliable estimate of RBA risk for most particle size changes. Three limitations to note: (1) asymmetric distributions, (2) shape and morphology of crystal, and (3) relationship between particle size and precipitation rate
Solid state form (<i>e.g.</i> , free base, salt, solvate, ...)	Simple to moderate	Complexity of change and impact on modeling strongly dependent on API properties. If baseline absorption of pure API is high, the change is less severe and modeling should provide reliable predictions. If baseline absorption of pure API is low, change is more severe and modeling will be less reliable
DIC to tablet or formulated capsule	Moderate to severe	These are the drug product changes most likely to produce surprising results. Mechanical properties could play important role in determining absorption and these are difficult to model. Also, excipients assumed to be inert could be source of secondary interactions that affect absorption, for example, impeding precipitation
Formulated capsule to tablet		
Tablet to formulated capsule		

DIC drug in capsule, API active pharmaceutical ingredient, RBA relative bioavailability

rating in the range simple to moderate. The actual severity and corresponding reliability level of the modeling depends on the properties of the API and how much they change as a result of the change in solid state form. The primary property that will be impacted is solubility, but other kinetic properties must be considered such as such as dissolution, supersaturation, and possibly precipitation. The physicochemical properties of the free base and HCl salt are shown in Table II. Table II shows that the gastric solubility of the two forms in fasted state is essentially identical, but the intestinal solubility of the HCl salt is slightly lower than the free base. This result is opposite to the more common situation where the salt has higher solubility as a result of modifying the pH, even in the situation where conversion back to the free base occurs or has more rapid dissolution. To test for conversion, the residual precipitate in the solubility assay was analyzed by X-ray powder diffraction (XRPD) for both the free base and HCl salt in aqueous media. The XRPD analyses revealed that both the free base and the HCl salt the crystal converted to an amorphous form. Note that it is important to recognize that it is not possible to know *a priori* if this *in vitro* conversion to amorphous observed would carry over to the *in vivo* situation. At the time of the RBA decision, there was no intrinsic dissolution data available for the HCl and free base. There was a dissolution comparison of the 80-mg strength capsules, but this was limited to pH2. The dissolution comparison revealed no significant difference in the dissolution characteristics of the two drug products. The difference in intestinal solubility may simply be experimental error or a kinetic effect (dissolution or precipitation), but since the solubility of the HCl salt was lower for all tests, the program team requested an assessment of the need for an RBA study under the default assumption that the solubility difference was real and could have an impact on the absorption of the HCl salt relative to the free base.

The first step of the modeling was to build an absorption model for the free base. The absorption of the free base forms

the baseline from which the relative performance of the HCl salt is assessed. The clinical data for the free base consisted of four doses in the fed state: 20, 40, 80, and 120 mg. GastroPlus® v7.0 was used to build and validate an absorption model for the free base. This was accomplished by building a model for the 20-mg dose and in turn validating this model by applying it to the three higher doses. A full description of the model building process is outside the scope of this short review, but a few important details will be provided here.

The fit of the free base model to the 20-mg dose is shown in Fig. 2. The predicted permeability for this compound (5) is $2.16 \times 10^{-4} \text{ cm s}^{-1}$. The optimized permeability for the free base absorption model is $2.0 \times 10^{-4} \text{ cm s}^{-1}$ and agrees well with the predicted value. The gastric solubility is high and essentially identical for both forms and therefore was not considered a critical model variable. The gastric solubility used in the 20-mg free base absorption model was 1.73 mg/mL. The intestinal solubility presented a problem that is often encountered in model building. The problem was that the 20-mg dose is basically too small to show any sensitivity to solubility. If a parameter does not show any sensitivity, it is not possible to optimize it. Sensitivity analysis showed that the 20-mg free base model had no sensitivity to intestinal solubility for values ranging from the lowest fasted state solubility up to the fed state solubility shown in Table II. One approach to this problem is to decrease the solubility until it shows an effect on Fa. This is the process of finding the minimum solubility. However, in this case, the minimum solubility would be much too low compared to the actual solubility and would produce error that would be amplified at higher doses. The large difference in fed and fasted state solubilities made this problem worse. Since the proposed RBA study would be run in the fasted state, it was decided to use the fasted state solubility and to use the higher of the two measured values. The higher intestinal solubility was used because it represented a more conservative approach for the comparison of the free base with the salt. The intestinal solubility used for the 20-mg free base model was 0.139 mg/mL. The results for the final 20 mg model with this solubility are shown in Fig. 2. Gastric emptying time was set to 1.25 h to simulate the fed state. Finally, no sensitivity to precipitation time was observed so the GastroPlus® default value of 900 s was used.

Table II. Physical–Chemical Properties and Solubilities of Free Base and HCl Salt

Property	Free base	HCl salt
clogP	5.152	–
Melting point	100.29°C	–
pKa (basic)	8.58	–
Predicted human intestinal permeability	$2.16 \times 10^{-4} \text{ cm s}^{-1}$	–
Aqueous solubility (pH)	0.01 mg/mL (7.3)	1.1 mg/mL (5.58)
Simulated gastric fluid solubility (pH) (SGF) ^a	1.724 mg/mL (2.32) >2 mg/mL (2.21)	0.75 mg/mL (2.5) 1.567 (2.03)
Simulated fasted intestinal fluid solubility (pH) (Fassif) ^b	0.069 mg/mL (6.49) 0.139 mg/mL (6.47)	0.03 mg/mL (6.51) 0.049 mg/mL (6.33)
Simulated fed intestinal fluid solubility (pH) (Fessif) ^c	>2.0 mg/mL (4.96)	1.47 mg/mL (5.1) >2.0 mg/mL (5.05)

^a 0.01 N HCl, 0.05% sodium lauryl sulfate, 0.2% NaCl

^b 29 mM NaH₂PO₄, 3 mM Na taurocholate, 0.75 mM lecithin, 103 mM NaCl, NaOH to pH6.5

^c 144 mM acetic acid, 15 mM Na taurocholate, 3.75 mM lecithin, 204 mM NaCl, NaOH to pH5.0

Fig. 2. Simulated and measured plasma concentration (C_p) profiles for free base at 20 mg. Model is described in the text

The model derived for the 20-mg dose was validated by applying it directly without any changes to the 40-, 80-, and 120-mg doses. The validation results are shown in Fig. 3 and it can be seen that the fit to the absorption phase is good for all of the validation doses. The fit is less accurate compared to the 20-mg dose but there is no obvious trend in the validation results, *i.e.*, C_{max} is not consistently under- or over-predicted. Parameter sensitivity analysis for the free base model showed that it is not sensitive to the precipitation time. As stated above, the dry blend ingredients for the test drug product were assumed to have no direct impact on solubility and dissolution but it may be possible for them to have an indirect impact on absorption by impeding precipitation. Because of this uncertainty, it was necessary to include precipitation time as a critical model variable. Precipitation time and intestinal solubility were identified as the two critical model variables.

The pharmacokinetic model used in the modeling should be briefly described. A simple one-compartment pharmacokinetic model was used and the parameters clearance and volume were optimized after obtaining estimates for the absorption parameters. The underprediction in the elimination phase observed for the 20-mg dose was also observed for the validation doses, but the magnitude and general shape of the discrepancy were consistent. The error in the elimination phase could be due to either underprediction of late phase absorption in the colon or multicompartment PK. The underprediction first appears at times beyond colon transit, so colonic absorption does not appear to be a likely source of the error. In addition, absorption for the 20-mg dose was predicted to be fairly rapid and complete ($F_a=100\%$), so if enterohepatic recirculation is not occurring, there would be no unabsorbed drug material remaining in the colon to be absorbed. The PK model could have been optimized to better fit the elimination phase, but this is difficult to do without

simultaneously impacting the absorption properties. Based on the assumption that a good absorption model had already been built, and that nothing really could be gained by optimizing the PK model, it was decided that the one-compartment model was sufficient for these purposes.

The protocol for the RBA study called for the two drug products to be compared at a dose of 80 mg in fasted state conditions but the possible upper limit of the dose of 300 mg could be required for future clinical dose studies. The response surface was calculated at 300 mg to evaluate the relative performance at this highest possible dose where differences are expected to be largest. The resultant F_a response surface at 300 mg is shown in Fig. 4. The 3D perspective of the response surface makes it slightly difficult to read, but close examination reveals that absorption of the HCl salt is predicted to be lower than the free base, and furthermore, the HCl salt is located on the down slope of the surface, where sensitivity is greatest.

The response surface compares the drug products at a single dose, but sensitivity to dose is also important to understand. Figure 5 shows a comparison of the dose-response curves for the two drug products. This graph demonstrates another important benefit of absorption modeling even when it is necessary to do an RBA study. For example, the absorption models could be used to reduce the relevant dose range and thereby design a more efficient RBA study. The graph in Fig. 5 shows that predicted exposure for the free base is linear with dose across the entire simulated dose range and agrees very well with the experimental data for 24 h AUC. In contrast, the dose-response curve for the HCl salt diverges from the free base and becomes nonlinear below a dose of 200 mg. At a dose of 300 mg, the exposure of the HCl salt is predicted to be approximately 75% of the free base, *i.e.*, a relative performance ratio of 0.75. Whether this

Fig. 3. Validation results for free base model at 40, 80, and 120 mg. Free base model was built on data for 20 mg and is shown in Fig. 2

Fig. 4. RBA Fa response surface at 300 mg showing position of free base and HCl salt

ratio means that the test drug product satisfies the standards for “similar enough” depends on the criteria established for the RBA study. In general, the criteria vary and furthermore are often interpreted loosely, unlike a bioequivalence where they are rigorous and interpreted strictly. The RBA criteria depend on factors such as therapeutic margin and dose sensitivity. For example, a narrow therapeutic margin would translate into tighter RBA criteria. Independent of any specific criteria, the modeling results suggest that there is significant risk that the exposure of the HCl salt drug product would be reduced compared to the free base. In addition to the reduced exposure, the location of the HCl salt on the steep part of the response surface increases the inherent

uncertainties in the modeling, effectively increasing the risk that exposure could be different. Overall, the modeling results would lead to the following recommendations. If exposure at a lower dose around 80 mg is the main concern, then an RBA study does not appear to be necessary. However, if the primary concern is exposure at higher doses around 300 mg, then an RBA study appears justified.

These recommendations appear to follow in a reasonably straightforward way from the modeling results, but different insights can be gained by looking beyond simple absorption outputs, such as exposure, and considering the details of the absorption process, in particular, what happens to the two drug products as they encounter the low pH environment of the stomach under fasted state conditions. Consider Fig. 6

Fig. 5. Exposure vs. dose–response curves for HCl salt and free base in fasted state conditions

Fig. 6. Simulated fraction of dose dissolved in stomach for HCl salt at gastric pH in fasted conditions (pH≈2)

which shows the simulated dissolution in the stomach for the HCl salt at doses of 350 and 400 mg in fasted state. The graph shows that based on the modeling, for the HCl salt at 350 mg, the dose is completely and rapidly dissolved in the stomach within just a few minutes. This implies that regardless of the API form, at fasted state gastric pH, the API will be completely dissolved in the stomach before it empties into the small intestine. Once the drug is completely dissolved, the solid state form of the drug product becomes immaterial. In the fasted state, regardless if it is the free base or HCl salt, it is basically as if the API was administered as a solution formulation.

This behavior revises the interpretation of the dose–response curve in Fig. 5 and in turn changes the recommendations. The correct interpretation is that in the fasted state, the two forms will follow the same dose–response curve. From a relative performance point of view, it does not matter which dose curve the drug products follow. This alternate interpretation of the dose–response curve strongly suggests that an RBA study would not be necessary, regardless of the dose. This conclusion, however, makes the very important assumption that the precipitation kinetics of the API are independent of the starting solid state form and any other excipients in the drug product. The dry blend for the HCl salt obviously contains the Cl^- counter ion and a few presumably inert components. In so far as the counter ion and inert components in the HCl salt dry blend do not inhibit precipitation, the two forms should have equal exposure.

The team concluded that the net risk was too high and decided to perform the study. A summary of the outcome of the RBA study is shown in Table III. As predicted, the two forms basically had identical exposures. One surprising result was that the higher in C_{max} observed for the HCl salt was statistically significant; however, it was also concluded that this difference in C_{max} did not have any clinical relevance and thus would not impact the dose for the HCl drug product. The slight difference in C_{max} could be due to slightly more slower precipitation time for the HCl salt but another possibility is that the form that precipitated from the HCl salt *in vivo* was redissolved more rapidly compared to the free base; for example, the free base could have precipitated as a crystal and the HCl salt as amorphous. While this is possible, it would be contrary to the *in vitro* results where both crystalline forms precipitated as amorphous.

Table III. Relative Bioavailability Study Results for Free Base and HCl Salt at 80 mg

	Geometric mean (CV%)	
	Free base	HCl salt
N	16	14
C_{max}	24.9 (27)	30.3 (33)
T_{max}	6.0 (2.0–12.0)	5.15 (2.0–8.0)
$t_{1/2}$	42.4 (21)	42.6 (21)
AUC (0–24 h)	359 (28)	413 (25)
CL/F (L/h)	82.1 (39)	74.3 (35)
Vz/F (L)	5,030 (34)	4,570 (25)

AUC area under curve

SUMMARY

Changes to the drug product are common along the development path of a molecule. With a change in the drug product often comes the question of the need to perform a RBA study. The primary purpose of the RBA study is to directly compare the two drug products and determine if the change to the drug product will alter the *in vivo* performance (AUC, C_{max} , and T_{max}) enough to require a dose adjustment or some other change to the administration protocol. Many of the RBA studies are unnecessary in the sense that the RBA studies reveal that the drug product changes are neutral, *i.e.*, the two drug products have equal or similar enough *in vivo* performance. Avoiding these unnecessary RBA studies represents a significant opportunity to improve the overall efficiency of drug product development. RBA risk assessment could help to do this by providing a rational understanding of the overall risk associated with not doing an RBA study. This paper discusses how to effectively use absorption modeling in the RBA risk assessment process. One limitation to absorption modeling in RBA risk assessment that must be accommodated is the inherent uncertainty associated with the modeling. The confidence level of the modeling should control how much weight the absorption modeling has in the RBA risk assessment calculation. The effective application of absorption modeling for RBA risk assessment therefore requires a general understanding of how the confidence level of the modeling varies with the drug product change and also how to build reliability directly into the modeling in order to maintain the confidence at the highest level given the available data package. Towards this goal, a set of four building blocks for effective absorption modeling in RBA risk assessment was proposed: (1) relate severity of drug product change and API properties to reliability of modeling, (2) use critical model variables to express the critical differences in the drug products, (3) generate a fraction-absorbed response surface expressed in terms of the critical model variables to evaluate the relative performance of the drug products, and (4) tie the first three building blocks together by following good model building practices that assure the highest quality model is built.

The four building blocks were demonstrated with a simple but informative example that described a change in solid state form from free base to HCl salt. The example demonstrated how an apparently simple drug product change could appear more complex and the importance of selecting the correct critical model variables. Using intestinal solubility and precipitation time as the critical model variables, the conclusion was made that there was substantial risk that the dry blended capsule of the HCl salt could have significantly lower exposure than the free base drug in capsule at the upper end of the proposed dose range. However, after reexamining the detailed simulated absorption behavior, it was concluded that both drug products were rapidly and completely dissolved in the stomach. This means that both drug products were effectively delivered as solution formulations and the intestinal solubility is not directly important to the absorption and should not be considered a critical model variable. The one critical model variable is precipitation time, and in so far as it is the same for both drug products, exposure for the two drug products should be identical. The results for the RBA study confirmed the modeling predictions

and revealed that the exposures for the two drug products were identical or basically similar enough to not warrant any dose adjustment or any other change to administration protocol. One curious result in the RBA study was that C_{max} for the HCl was higher than the free base. While this difference was statistically significant, it was deemed not to be clinically relevant.

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