An assessment of occasional bio-inequivalence for BCS1 and BCS3 drugs: what are the underlying reasons?

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Abstract

Despite having adequate solubility properties, bioequivalence (BE) studies performed on immediate release formulations containing BCS1/3 drugs occasionally fail. By systematically evaluating a set of 17 soluble drugs where unexpected BE failures have been reported and comparing to a set of 29 drugs where no such reports have been documented, a broad assessment of the risk factors leading to BE failure was performed. BE failures for BCS1/3 drugs were predominantly related to changes in C_{max} rather than AUC. C_{max} changes were typically modest, with minimal clinical significance for most drugs. Overall, drugs with a sharp plasma peak were identified as a key factor in BE failure risk. A new pharmacokinetic term ($t½C_{max}$) is proposed to identify drugs at higher risk due to their peak plasma profile shape. In addition, the analysis revealed that weak acids, and drugs with particularly high gastric solubility are potentially more vulnerable to BE failure, particularly when these features are combined with a sharp C_{max} peak. BCS3 drugs, which are often characterised as being more vulnerable to BE failure due to their potential for permeation and transit to be altered, particularly by excipient change, were not in general at greater risk of BE failures. These findings will help to inform how biowaivers may be optimally applied in the future.

1. Introduction

The biopharmaceutics classification system (BCS) has proven to be an effective tool for biowaivers, demonstrating that rapidly dissolving immediate release oral products of soluble drugs are likely to perform similarly in-vivo, eliminating the need for human bioequivalence studies[1].

In the BCS rationale, bioequivalence (BE) of highly soluble, highly permeable drugs (BCS1) is assured provided product dissolution is rapid (>85% in 30mins) under mild agitation in a standardised compendial paddle or basket method, as dissolution is not then the rate limiting step in drug absorption[2]. Dissolution profile similarity provides additional assurance. A similar rationale applies to BCS3 drugs, albeit with a tighter requirement for very rapid dissolution (>85% in 15 mins). Low permeability drugs are perceived to be at higher risk as they are more likely to exhibit a restricted absorption window in the upper GI tract[3], making their pharmacokinetics more vulnerable to changes in transit time[4]. In addition, for a permeability limited drug, changes in luminal drug and excipient concentration may influence absorption, as according to the concepts described in the BCS aligned Biopharmaceutics drug disposition classification system (BDDCS)[5], absorption is more likely to depend on active uptake and efflux mechanisms. Some categories of excipients, such as non-ionic surfactants, may interact with these active processes[6].

Recently, an ICH harmonisation process led to globally harmonised guidance for BCS based biowaivers[7]. Although having globally harmonised BCS guidance is a welcome step, concerns have been expressed that the guidance in its current form is overly conservative in some aspects, such as strict dissolution requirements and the strict limits applied to excipient change[8-10]. There is therefore scope to improve and expand BCS biowaiver guidance in the future, based upon an improved scientific understanding of specific bioequivalence risks.

The FDA defines bioequivalence as “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study”[11]. Unless a biowaiver can be justified, for a new immediate release test product to be considered bioequivalent, demonstration of similarity of C_{max} and AUC to within 80-125% of an existing reference product in a human crossover study is typically required. Most BE studies have historically been performed in the fasted state, which is generally considered more sensitive to formulation changes[12].

Previous retrospective analyses of BE study success rates have demonstrated the logic for BCS biowaivers is broadly sound. Cristofoletti et al[13] showed that in a study of 500 BE studies in data

submitted to the regulatory agencies in Brazil, BCS2 drugs were much more likely to fail than BCS1/3 drugs. Specific drug names and detailed properties are not provided, but overall, 16% of studies with BCS 1 drugs and 9% with BCS 3 drugs failed in BE studies, far fewer than the 40% failure rate for BCS2 drugs. When further accounting for similarity/dissimilarity in the Quality Control (QC) dissolution test, only about 10% of studies involving soluble drugs failed unexpectedly, i.e. the negative outcome could not have been anticipated from the QC dissolution data. Most of the BE failures for BCS1/3 drugs were for C_{max} only (18 out of 22 failures).

Similarly, Ramirez et al[14] studied a smaller set of 124 BE study submissions in Spain and identified BE failures for BCS 1/3 drugs pravastatin, zolpidem, codeine, isoniazid, ranitidine and lisinopril. As some drugs used in this evaluation were either unclassified or misclassified, after reassessment of BCS class, bromazepam, clavulanic acid, pentoxifylline and risperidone can also be identified from this work as likely BCS1/3 drugs with reported BE failures.

Further examples of occasional BE failure for BCS1/3 drugs can be found in the International Pharmaceutical Federation (FIP) biowaiver monograph series[15] for solid oral dosage forms, where published BE study outcomes for each drug are listed. Examples include lamivudine[16], enalapril[17], zidovudine[18], and acetylsalicylic acid[19]. Verapamil, assessed in one of the earliest biowaiver monographs where a list of literature BE studies was not included in the monograph paper[20], was also identified as being vulnerable to BE failure[21,22]. Additional examples where BCS1/3 drugs failed bioequivalence, and outcomes were predictable from dissolution studies (e.g. non-similarity), have been reported for amoxicillin[23], prednisone[24], metronidazole[25], quinine and quinidine[26].

Elsewhere, Garcia-Arieta et al studied BCS1 and 3 failures from a regulatory perspective in a series of papers, highlighting various BCS1/3 drugs that appear vulnerable to failed BE studies [27-30]. The focus of these papers is on the potential impact of excipients on bioequivalence, and on dissolution conditions to improve the detection of inequivalent products. Drugs highlighted included risperidone[30], lamivudine[30], dexketoprofen[27], pravastatin[28], zolpidem[29] and alendronic acid[30].

By studying these examples as a group, the properties of drugs that are most at risk of bioequivalence failure could be examined, trends can be sought and additional risk factors for bioequivalence could be identified.

Specifically, the present analysis was designed to assess:

a) Does the sharpness of the absorption peak influence the risk of bioequivalence?
b) Can recent insights into inhomogeneous mixing in the fasted state in the upper GI tract[31] help to understand the risk of inequivalence for soluble drugs?

2. Methods

A set of 11 BCS 1 and 6 BCS 3 drugs where unexpected bio-inequivalence between nominally similar oral formulations has been reported by Cristofoletti et al[13], Ramirez et al[14], or in the biowaiver monograph series were identified (see Table 1). Drugs where changes in bioavailability were correlated to in-vitro data were also noted, but not included in this set. Properties of the drugs which may contribute to a higher risk of unexpected BE failure were captured, including the key indicators for this work, $t½C_{max}$ (as an indicator of peak sharpness) and gastric solubility.

The concept of $t½C_{max}$ is demonstrated in Figure 1. It is the time from dosing to the point in the plasma profile where drug concentrations fall to half that of C_{max} and designed as a measure of the sharpness of the plasma profile peak. $t½C_{max}$ was estimated for each drug from representative graphical plots of the mean plasma profile from single dose fasted human PK studies identified in the literature. Drugs with a $t½C_{max}$ of less than 5hrs were categorised as having a "sharp" plasma profile, whilst those >5hrs were classed as displaying a "blunt" plasma profile. The 5hr cut off was selected on the assumption that dissolution of a soluble BCS1/3 drug in an immediate release formulation in-vivo will predominantly occur in the first 1-2hrs after fasted administration, and as a result, if $t½C_{max}$ >5hrs, the impact of small changes in dissolution will have significantly less influence C_{max}. Note that this assumption is uniquely useful for BCS1/3 drugs - for poorly soluble drugs, dissolution is likely to continue over a more prolonged time in the GI tract.

Paracetamol was selected as a borderline drug for determining whether a drug has very high solubility (gastric solubility = 20mg/ml[12]). Paracetamol is a suitable borderline drug as its pharmacokinetic profile (especially onset) can be manipulated via deliberate formulation change[32,33], but there are no reports of unexpected bio-inequivalence [34].

The 17 test drugs were then compared to a larger set of 29 reference immediate release (IR) drug products (18 BCS 1, 11 BCS3) where unexpected BE failures have not been reported (see Table 2). This set was gathered from BCS1/3 drugs identified from the FIP biowaiver monograph series, as for these examples the research done for each manuscript in the monograph series[15], which includes tracing of reported BE study results, provides a useful list of BCS1/3 drugs where unexpected BE failure is likely to be very low.

3. Results

Figure 2 lists the BE failures identified, highlighting the failure mode (AUC and/or C_{max}) and classified by gastric solubility and t½C_{max}.

Of the 17 drugs where BE failures were reported, 7 failed for both AUC and C_{max}, 1 failed for AUC only, and 9 failed for C_{max} only. Overall, BE failures for BCS1/3 drugs were more commonly as a result of changes in C_{max} than AUC (16 occurrences versus 8). Excluding known to be inadequately powered studies, C_{max} failures outnumbered AUC failures by 9 to 3. For the 8 drugs where AUC had changed, underpowering, or other specific factors could mostly be identified that likely contributed to their inequivalence (see discussion).

Where actual comparative statistical BE data was available (13 BE studies on 9 of the test drugs), C_{max} failures were typically marginal, with the test product point estimate within 80-125% of the reference product for 11 out of the 13 BE failures.

BCS1/3 drugs were more likely to exhibit bioequivalence failures if they had a short t½C_{max} and high gastric solubility. Short t½C_{max} appears a particularly good indicator for BE failure risk.

Although analysis is hampered by the small number of examples in each case, several additional subcategories of BCS1/3 drugs where BE risks may be higher could be identified:

a) Weak acids (which may not fully dissolve in the stomach, even though soluble in <250ml)
b) Drugs which display extensive gastric instability, e.g. clavulanic acid,
c) Drugs which are extremely poorly absorbed (e.g. alendronic acid, FA<1%)
d) Drugs with extensive first pass metabolism (e.g. verapamil)

In alignment with the data gathered by Cristofelli et al[13], with the notable exception of the significant changes in PK for alendronic acid, there was no evidence that low permeability (BCS 3) drugs are more vulnerable to biowaiver failure than high permeability (BCS 1) drugs. Indeed, for the occasional cases where BE for the test product based upon the point estimate were outside 80-125% of the reference, these were BCS1 drugs.

The evaluation of the risk of high gastric solubility is confounded somewhat by the weak acids in the data set, which tended to have a higher risk of BE failure, but lower gastric solubility. Assessment of the data set without weak acids present gives a clearer signal for the potential risk of high gastric solubility.

4. Discussion

The potential causes for BE failures for BCS1/3 drugs are many and varied. Some are related to the properties of the drug or the formulation, whilst others may relate to specific issues with the study design, how the study was conducted, or dosing. The most obvious study design related reason is when there is an inadequate number of volunteers used (underpowering). In the assessment of Ramirez et al[14], for more than half the BCS1/3 BE failures identified (5/9), retrospective assessment of the variability in the PK data demonstrated underpowering was a factor. However, it is important to note that unexpected PK variability observed in a BE study could in some cases still be test or reference product property related.

Beyond inadequate powering, there are several potential risk factors leading to BE failure for BCS 1/3 drugs, some of which have been discussed previously in the literature. These include:

1) Rapid elimination [4,9,29,35]
2) Inability of the in-vitro dissolution test to detect in-vivo relevant changes [27 29]
3) Changing the levels of absorption modifying excipients in the formulation [28,30,35,36]
4) Low permeability [4,14,37]
5) Extensive first pass metabolism[9,22]

4.1. BE Failures related to peak sharpness ($t½C_{max}$), and gastric solubility

In this analysis, drugs were categorised as to whether their $t½C_{max}$ was sharp or blunt depending on whether it was greater than or less than 5hrs. To determine this, fasted state single dose human pharmacokinetics of a representative immediate release solid oral drug product was identified from literature. It's worth noting that for some drugs there is ~~some~~ formulation dependent study to study variability in $t½C_{max}$, for instance when a drug is administered as a solid dosage form versus a solution. However, this variability is markedly less for soluble drugs, as slow in-vivo dissolution is far less likely to influence pharmacokinetics. It was also possible to minimise $t½C_{max}$ variability for this analysis by focussing on solid oral dose studies only.

As already identified in the literature, rapid elimination, especially during the initial elimination phase, makes the C_{max} peak sharper, and therefore more vulnerable to changes in absorption kinetics. For many drugs, especially where there is biphasic elimination, the initial decline (alpha phase) may actually depend primarily on distribution kinetics[35]. A similar, perhaps counterintuitive risk factor to C_{max} equivalence is absorption rate. Rapid absorption is generally associated with good permeability, and therefore lower BE risk, but ~~very~~ rapidly absorbed drugs also have a sharper plasma peak, and therefore may be more vulnerable to BE failure. $t½C_{max}$ captures both absorption and initial

elimination rate. The vulnerability of these drugs to BE failure linked to subtle changes in dissolution is discussed below, however one further consideration is that to optimally characterise a sharp C_{max} peak, more frequent PK sampling may be needed. The drugs in our analysis with most marked changes in C_{max} were highly permeable weak acids (acetyl salicylic acid, and dexketoprofen) with very short $t½C_{max}$.

The impact of t½Cmax on the risk of fasted state BE failure is linked to gastric emptying kinetics, which is in turn dependent on the migrating motor complex (MMC), the cyclic, recurring three phase motility pattern which controls fasted state transit. This interdependence has been modelled in the work of Talattof et al [4], who investigated BCS1/3 drug BE failure risk using a "motility-dependent compartmental absorption and transit" modelling approach. Their work demonstrated that drugs with a rapid elimination half-life were more likely to display gastric emptying dependent pharmacokinetics, and an increased risk of BE failure. Interestingly, their work also demonstrated gastric fluid volumes, and whether a BCS3 drug had a narrow window for absorption were also important factors in BE failure risk assessment. However, the impact of non-homogeneous motility phase dependent mixing on dissolution in the stomach was not specifically assessed.

Another counterintuitive risk to BE failure explored in this work is that of gastric solubility. The rationale for it being a risk factor is based upon emerging understanding of the inhomogeneous mixing kinetics in the fasted stomach after a dosage form is taken with a standard 240-250ml glass of water (see below). When gastric drug solubility was equal to or greater than paracetamol, the risk of BE failure increased. The combination of high gastric solubility and sharp C_{max} peak was identified as a particularly risky combination for C_{max} failure, seen for 12 out of 16 of the drugs in the test set where BE failures for C_{max} had been reported. If weak acids were eliminated from the set, then the trend became even more obvious, with 10 out of 11 C_{max} failing non-acid drugs having this combination of risk factors.

The reason why very highly soluble drugs may be at greater risk of inequivalence, especially for C_{max} can be drawn from recent insights in stomach/duodenal fasted state motility and mixing from human intubation and aspiration studies[38,39]. Incomplete mixing of gastric contents prior to gastric emptying has for instance been assumed after solution dosing of paromomycin[40]. In a follow-up study, incomplete mixing was confirmed upon oral administration of paromomycin (250 mg tablet); gastric motility appeared to play a critical role in determining the degree to which the administered drug and the residual gastric volume mixed: the drug was more homogenously distributed in the stomach when it was administered during a period of gastric contractile activity (phase II of the MMC) as in the absence of gastric contractile activity (phase I of the MMC)[41]. Variability in PK caused by the cyclic

motility pattern was confirmed with an immediate release tablet of fosamprenavir[42]. The intragastric disintegration of the tablet was faster and less variable after administration during phase II of the MMC, resulting in faster and less variable absorption of amprenavir. If a rapidly disintegrating formulation of a soluble drug is taken in the fasted state (phase I of the MMC), drug intake with sparkling water (bicarbonate effect) resulted in a trend toward faster and less variable absorption of paracetamol from the gastrointestinal tract[43]. These studies clearly identified the time of oral drug intake relative to the inter-digestive motility pattern as an important source of variability in drug PK.

In contrast to previous assumptions, where the gastric dissolution of BCS1 drugs was thought to be assured by rapid and close to complete dissolution in the stomach, these recent insights provide a rationale for how very highly soluble drugs in rapidly disintegrating formulations may exhibit some motility phase dependent variability in their dissolved concentrations in the upper GI tract. For most drugs, small variations in dissolved drug concentrations from one formulation to another within the first hour or so after administration will have negligible impact on pharmacokinetics. However, for drugs with a short t½C_{max}, these differences could lead to small changes in C_{max}.

These differences between the dissolution behaviour of formulations are likely to be most apparent when contractile activity is slow. Currently available in-vitro tools used to de-risk BE studies as recommended in BCS biowaiver guidance to date are limited to compendial paddle and basket set ups, with volumes of between 500-900ml typically used. These tests may not always be capable of detecting dissolution differences under low agitation in lower volumes. Even when lower agitation rates are attempted, in-vitro artefacts in the compendial test method, such as coning, tend to hinder their efficient use. Interestingly, when new formulations of very rapidly dissolving paracetamol were developed, using bicarbonate to boost initial dissolution rate in the fasted stomach, a 30rpm paddle method was found to be predictive[44]. Similarly, 30rpm was recommended for detecting differences in the performance of zolpidem tablets[29]. Unfortunately, the number of oral solid dose products where it is possible to use such low rotation speeds below 50rpm in a compendial set up without coning or similar in-vitro issues is likely to be very limited. Modified vessels to eliminate coning but keep the rotation speed low have been proposed[45] and could be one option for de-risking BE studies to differences in low agitation dissolution kinetics. These, and other emerging biorelevant in-vitro tools for assessing formulations under in-vivo relevant conditions[46-48] may be useful when considering the dissolution options in the future for the justification of biowaivers.

In view of the impact motility may have on disintegration and dissolution, several of these emerging new tools have been developed/optimised to explore motility effects in vitro. For a discussion of various biorelevant in vitro dissolution tools able to simulate human peristalsis [e.g. Dissolution

StressTest device, Dynamic Open Flow-Through Test Apparatus (DOFTA), TIM-agc (agc = advanced gastric compartment)], we refer to a recent review on in vitro models for the prediction of in vivo performance of oral dosage forms[47]. Separately, the dexketoprofen BE failures [27] have been studied using the Gastro-Intestinal simulator (GIS) model, producing good evidence that predictability of the dissolution differences influencing pharmacokinetics is possible[49]. This work demonstrated that the changes in C_{max} were likely to be related to the rate and extent of disproportion of the dexketoprofen trometamol salt to its free acid in the stomach.

Dexketoprofen and acetylsalicylic acid, both BCS1 weak acids with a short t½C_{max} but lower gastric solubility than paracetamol, appear particularly vulnerable to C_{max} BE failure[27]. Subtle differences in the extent of dissolution at gastric emptying may be contributing to this vulnerability, despite the observation that these drugs are robust to changes in AUC, to a degree of confidence where biowaivers for weak acids with good intestinal solubility have been proposed[50]. Further supporting evidence for weak acids being vulnerable to C_{max} change comes from data on BCS2 weak acids such as ibuprofen, ketoprofen and diclofenac, which are known to be C_{max} (but not AUC) sensitive, despite having good intestinal solubility [50-54]. Their incomplete gastric dissolution, which is more marked due to their BCS2 classification, is likely to be an important factor. For BCS1 weak acids, even if soluble at saturation in 250ml of gastric media, the combined effects of variable fasted motility and the rapid emptying dynamics of administered water after intake[55] is likely to mean dissolution is incomplete at the point of gastric emptying, leading to similar C_{max} vulnerabilities to BCS2 weak acids.

Therefore, whilst underpowering can be assumed to be a relatively common cause of BE failures for BCS1/3 drugs, this work indicates another likely reason for a BCS1/3 BE study to fail is due to difficult to detect dissolution differences when the plasma peak is sharp. The currently employed in-vitro tests may inadequately detect these differences occurring in poorly mixed environments in the stomach and upper small intestine.

4.2. BE failures related to small changes in excipient levels

The impact of excipients on the pharmacokinetics of BCS1/3 drugs is a subject which has caused much controversy in the literature, with advocates on one side of the debate some pointing to data where small changes in excipient levels were correlated with PK change in human BE studies[29,30,56], data from cell line measurements[57-61] or in-situ animal perfusion studies[57,62] where excipients have altered drug permeability as evidence that even small changes in excipient levels can lead to inequivalence. According to this position, BCS3 drugs are at greater risk of BE failure from small excipient level changes (see section 4.4 for a more general discussion on low permeability impact).

On the other side of the debate protagonists argue the impact of small changes in excipient levels on pharmacokinetics of BCS3 drugs is minimal, and point to evidence from:

(1) targeted human studies on the effect of common excipients on BCS3 drugs[63,64],

(2) examples where absorption enhancing excipients have failed to improve human PK [65,66]

(3) preclinical perfusion studies performed at relevant excipient and drug concentrations[67]

(4) assessment of BE risks that have been performed with the theoretically high-risk BCS3 drug metformin[10]

In addition they argue, the use of cell line data and even perfusion studies have many caveats regarding their use as predictive methods for excipient effects in humans[68,69].

There is broad agreement, based upon established scientific evidence of excipient influence when the level of excipient change is high for excipient that is known to alter transit time, and the drug in question is a low permeability drug vulnerable to changes in GI transit time[35,36]. Similarly, there is evidence that excipients may, if administered in high enough levels, influence efflux mechanisms to alter human pharmacokinetics[36,70,71]. These changes are more likely to be significant at levels present in liquid formulations (>>100mg of excipient) than solid oral dosage forms. The controversy regarding excipient impact is therefore focussed on whether relatively small changes in excipient levels (~100mg or less), typical level of change when developing solid oral dosage forms, impact human pharmacokinetics. Whilst this controversy is likely to continue to be a source of debate, the evidence gathered from this analysis suggests that small changes in dissolution for solid oral dosage forms under low agitation in the upper GI tract is the more likely reason for most unexpected BCS1/3 BE failures in adequately powered studies, with these failures more likely for certain sub-categories, such as those with a sharp C_{max} peak.

Currently in the ICH M9 biowaiver guidance, excipient risks are treated slightly differently according to whether the drug is BCS1 or BCS3, and whether excipients are known to be absorption altering[7], with tightness of the allowable level of change as a percentage of the excipient level dependent on this categorisation. Others have recently argued for more nuanced excipient classification to capture the risks relative to the nature of the excipient[72]. Even so, there is little consideration in these schemes for the actual concentrations of excipients present in solution at the gut wall, which is a pre-requisite for most of the proposed mechanisms for excipient mediated effects on BE. These concentrations will be low for most excipients after administration of typical solid oral dose forms.

Although no trend to an increased risk of inequivalence is seen in our assessment, the oral absorption of poorly permeable BCS 3 drugs is complex, with a stronger dependence on transit time and GI region dependent permeability than for highly permeable drugs due to slower absorption being spread over a larger proportion of the GI tract. Given this complexity, physiologically based pharmacokinetic modelling (PBPK) may be especially useful in determining factors influencing their absorption and therefore could prove to be an invaluable tool for future assessment of excipient change on pharmacokinetic performance[73].

4.3. BE failure relating to gastric instability

Clavulanic acid appears vulnerable to BE failure due to a combination of a sharp plasma peak and rapid gastric degradation[74,75]. This latter factor adds another variable to the factors influencing the pharmacokinetic profile. Dissolution differences would be magnified by subsequent degradation, likely affect both C_{max} and AUC, whilst even if formulations displayed similar dissolution behaviour, degradation would likely add significant variability in drug availability for absorption, reducing the probability of BE. Instability also is likely to be the reason why it was not possible to find gastric solubility of clavulanic acid in the literature; gross instability makes it too challenging to measure. The high reported water solubility is enough to make it highly likely it meets the BCS criteria for high solubility, however the assignation of gastric solubility category in this work is somewhat uncertain.

Similarly, pravastatin has been reported to be vulnerable to rapid gastric degradation[76]. For instance, significant degradation within in-vivo relevant time frames at pH 3.0 / 40^{o}C have been reported[77].

For the pravastatin BE failure example, C_{max} is altered, but AUC is unchanged. In the detailed study by Ruiz-Picazo et al[28] on pravastatin BE failure, the potential for gastric degradation as a contribution to BE failure is not mentioned, although it has been reported elsewhere that generation of low pH dissolution data was not possible as a result of the degradation kinetics[76]. The propensity of pravastatin for gastric degradation is the likely explanation for the marked difference in the reported solubility values at pH1.2 in these two papers, and may have compromised the ability of the dissolution test to detect differences between the formulations studied by Ruiz-Picazo et al[28]. Therefore, there is reason to doubt their conclusion that small changes in excipients alter the C_{max} of pravastatin, even with the supporting cell line data with the excipients used in the tablet formulation. Further questions on the conclusions of Ruiz-Picazo et al[28] stem from the observation that most of the excipients in the studied tablet formulations listed are insoluble and therefore unlikely to be capable of altering permeability, and neither of the soluble excipients, lactose and povidine are likely to influence motility or permeability at levels used in a standard tablet formulation. Subtle differences in dissolution under low agitation (as also highlighted by Ruiz-Picazo et al), perhaps magnified (and

disguised when trying to detect it in-vitro) by drug degradation, may offer an alternative explanation for the non-equivalence of pravastatin in this case.

Rapid degradation may also make other aspects of BE and biowaivers more challenging and potentially more variable, such as the stability of the drug product prior to administration, generation of reliable solubility and dissolution data, and the handling of bioanalytical plasma samples taken during a BE study.

4.4. BE failure relating to extreme low permeability

Alendronic acid may be rationalised as more vulnerable than a typical BCS3 drug to BE failure due to its extremely low permeability (~1% absorbed), combined with a limited absorption window[78]. The modelling work by Yamane et al[35] highlights that the impact of sugar alcohol induced transit time may be increased for this category of drug. Even so, the robustness of the data for the failed BE study, which failed by a significant margin as reported by Garcia-Arieta et al[30] has been questioned by others, as the test product manufacturer subsequently managed to market a bioequivalent product containing the key excipient proposed to be altering permeation, sodium lauryl sulphate[64]. Irrespective of the validity of that particular set of study data, other studies have shown that alendronic acid's pharmacokinetics is prone to change from co-dosing with even small amounts of food[79], suggesting there is a real vulnerability to PK change in the presence of other materials in-vivo which have the potential to interact with dissolved drug, altering drug uptake.

Although in general, low permeability does not appear to increase BE failure risk, at the extreme end of the low permeation range of oral drugs a very limited window in the GI tract for absorption can be expected, which means there is potential for even small microenvironmental changes and interactions with co-administered materials to alter drug availability for permeation. Oral drugs with such low permeability are uncommon, and more data is needed on their PK vulnerabilities. Acyclovir is a drug with relatively low fraction absorbed (10-30%)[80], albeit significantly higher than alendronic acid, which has been shown to be insensitive to significant changes in common excipient levels[63], indicating that a fraction absorbed cut off below which poor permeability becomes a significant risk for BE failure would likely be at a level which does not affect most BCS3 drugs.

Even so, as new, low permeability oral peptides and proteins such as the excipient enhanced peptides semaglutide and octreotide are now reaching the market[81], the number of extremely low fraction absorbed oral drug products is expanding. These drugs have very limited absorption windows (for semaglutide its excipient enabled absorption window is in the stomach[82]). Such drugs are likely to be

poor candidates for BCS biowaivers, even though they may meet current BCS class 3 classification requirements.

4.5. BE failure relating to extensive first pass metabolism

Verapamil is a drug with extensive first pass metabolism and high PK variability[83], and adequate powering is likely to be a significant factor behind the couple of failed studies found in the literature[22]. High levels of first pass metabolism have previously been identified as a potential risk factor for BE[9], but it is unclear whether this is just as a result of higher PK variability in general, or whether there are specific additional factors at play, such as drug concentration dependent saturation of first pass metabolism. In the two data sets used for this work, extensively first pass metabolised drugs appear in both the set with BE failures (verapamil, pentoxifylline, pravastatin, risperidone), but also feature to some extent in the reference set with no unexpected BE failures (propranolol, ribavirin, prednisone). Further work is therefore needed to fully understand the relationship between first pass metabolism and BE risk.

4.6. Specific comments for other BE failure example drugs

Codeine was included in the test set as it was identified from the data from Ramirez et al[14], and was included in this analysis for completeness. However Colon-Useche et al[29] have subsequently indicated that there were likely to have been specific issues with this BE failure case. It was co-formulated with Ibuprofen, and atypically, Ibuprofen also failed to show equivalence for AUC to the single entity tablets. Codeine also has the added complication that it slows gastric emptying[84]. It is also worth noting that all drugs in combination products need to meet the BCS 1/3 criteria for a combination product to be in scope for a biowaiver[7].

Similarly, isoniazid was also included in our data set, even though Colon-Useche et al[29] indicated that the change in filler used in the tablets from the test to the reference (most likely from lactose) to mannitol is the likely explanation for the BE failure. However, the properties of isoniazid, which has excellent gastric solubility and a sharp C_{max} peak, mean that alternative explanations, such as sensitivity to changes in dissolution under low agitation should not be ruled out. If the switch in filler was from lactose to mannitol, another possible reason for the lack of equivalence is highlighted in the biowaiver monograph paper for isoniazid, as it is prone to chemical degradation in the presence of lactose[85]

The risperidone BE example was taken from Garcia-Arieta et al[30], using an example where two oral solid dosage forms have been compared [30]. Other examples from this paper where solution formulations were used were not included in this analysis, as solid oral dosage forms were the focus

of this assessment. In the work of Garcia-Arieta et al, changes in certain excipients were identified as factors thought likely to be responsible for the BE failure. Again, this analysis indicates the good gastric solubility and sharp C_{max} peak of risperidone means there may be other possible explanations, beyond the influence of excipients for the observed non-equivalence. Like several of the other examples, more details of this study are not published in the literature, which makes definitive interpretation difficult.

The reasons for the bio-inequivalence of lisinopril, pentoxifylline and bromazepam are also somewhat unclear, as no study details are available. However, Ramirez et al[14] identified underpowering as an issue for the lisinopril and pentoxifylline BE study. In addition, pentoxifylline has a remarkably short t½C_{max} and like verapamil is extensively first pass metabolised. Bromazepam, a low dose drug, has a low enough solubility over most of the physiological pH range for dissolution rate to potentially be a factor in determining BE[86]. Indeed, an additional potential class for BE failures for BCS1/3 drugs are drugs that meet the dose/solubility criteria for high solubility, but only because their dose is extremely low. Digoxin, which is known to be dissolution rate sensitive has previously been discussed in this context[87]. It is likely that this sub class of BCS1/3 drugs usually do not typically fail BE studies because their dissolution rate sensitivity is ideally suited to pre-study detection with standard dissolution methods. Dissolution rate sensitivity for bromazepam could, however, be missed if dissolution was only performed at pH1.2, the only point in the physiological range where the drug solubility is very good[86], but which is too low for typical fasted gastric pH after dosing with a glass of water[88].

5. Conclusions

Unexpected BCS 1 and 3 BE failures, although relatively rare, relate to C_{max} change more frequently than AUC.

In most cases where BE failures are reported, the changes in C_{max} are small (point estimates within 80-125%), at levels that are unlikely to be of clinical relevance.

Many of the BCS1 and 3 drugs that have reported BE failures had two distinct properties:

1) A sharp plasma peak, characterised by a short t½ C_{max}
2) Remarkably good (better than paracetamol) solubility at pH typical of gastric conditions

A plausible hypothesis is that a sharp plasma peak profile creates the potential for PK sensitivity to the initial in-vivo dissolution rate, whilst excellent drug solubility in the stomach means significant drug dissolution occurs under very mild motility conditions, thus partially accessing co-administered fasted water in a manner atypical for other (less soluble) drugs.

Weak acids, which may only partially dissolve in the stomach, despite having BCS1/3 solubility properties, are a specific sub-category of BCS1/3 with greater risk of C_{max} related BE failure.

Extensive upper GI tract degradation, extensive first pass metabolism, and a very limited window for drug absorption, characteristic of drugs with an extremely low fraction absorbed, may also be risk factors for BE failure.

There is no evidence that BCS 3 drugs in general are at higher risk of inequivalence than BCS 1 drugs, despite their greater sensitivity to transit time and active uptake and efflux processes. This means the hypothesis that small changes in excipients levels is a leading cause of BE failure as postulated in some of the work by Garcia-Arieta et al, appears a less likely cause of BE failures. If this were the case, low permeability, efflux and active uptake affinity, would be apparent in this analysis. The lack of an influence of sugar alcohols on intestinal transit times at levels below 600mg has already been demonstrated[35]. Further work may be still needed to mechanistically demonstrate realistic no effect levels of excipient influence on other possible PK altering mechanisms, but overall, there is scope to relax the current very tight limits on excipients in biowaiver guidance.

With remarkably few exceptions, the BCS biowaiver criteria appear to be robust. The vulnerability of a small subset of BCS1/3 drugs to BE failures is mostly characterised by small changes in C_{max} that are unlikely to be of clinical significance. Nevertheless, to further bolster confidence in the BCS biowaiver approach, improved biorelevant in-vitro dissolution approaches targeting behaviour in poorly mixed environments in the upper GI tract may be particularly useful for drugs with a short $t½C_{max}$.

Whilst care is needed with drugs with a sharp C_{max} peak, for drugs with a $t½C_{max}$ of >5hr, there is a case for greater regulatory flexibility for biowaivers. For these drugs, complete dissolution in 30mins rather than 15 irrespective of permeability class, and the flexibility to allow higher paddle/basket rotation speeds during BCS biowaiver dissolution testing to overcome coning may for instance, be justifiable.

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Figure 1: Illustration of how t½C_{max} is determined from a mean plasma profile

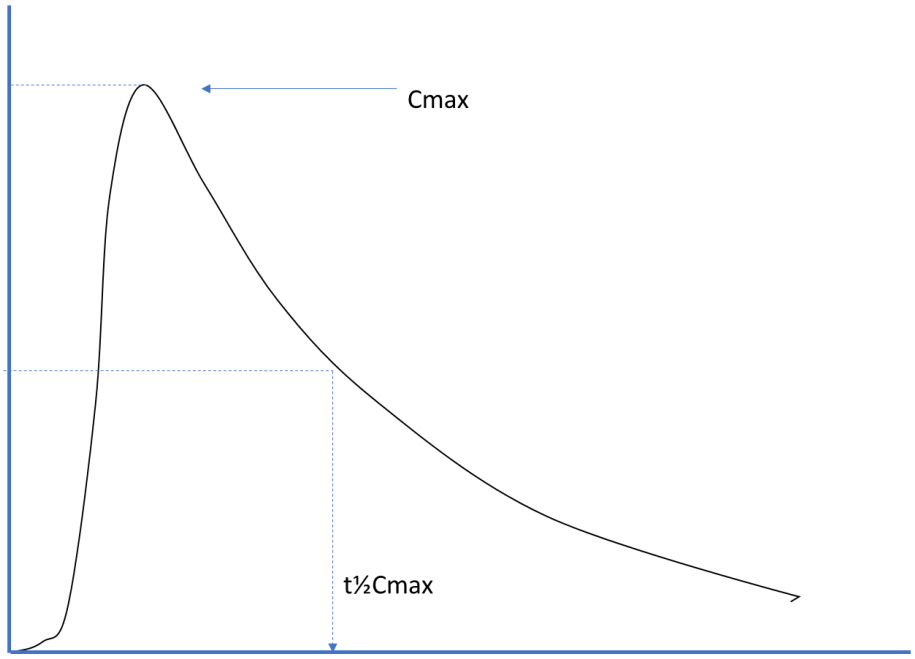

Figure 2: BCS1/3 BE failure categorised by gastric solubility and peak sharpness

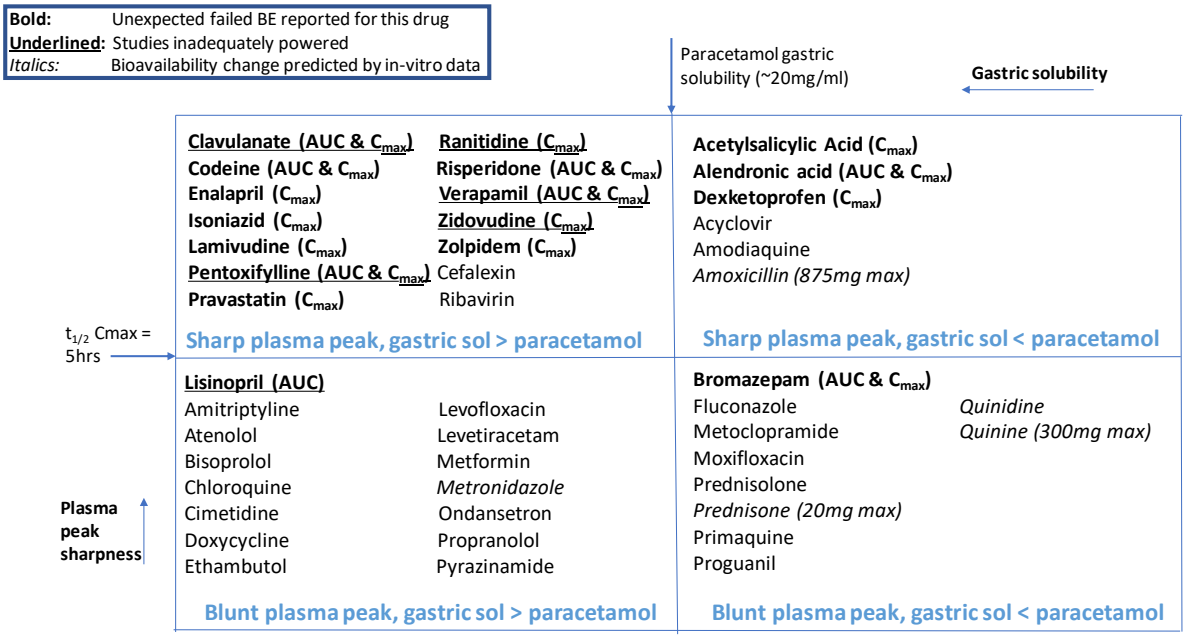

Table 1 Properties of 17 BCS 1/3 drugs where BE failures have been reported, plus Paracetamol

Drug	**BCS class**	**Highest Dose Strength (mg)**	**Ionisation type**	**Solubility in gastric media pH1.2 (mg/ml)**	**Solubility in Intestinal media pH6.8 (mg/ml)**	**t½ C_{max}**	**Failure mode**	**C_{max} Point estimate deviation (%)**
Acetylsalicylic acid*	1	500	A	4.7[19]	7.6[19]	0.8[89]	**C_{max}**	38[89]
Alendronic acid	3	70	A	10-20[90]	>20[90]	3.0[91]	**AUC/ C_{max}**	>20[30]
Bromazepam	1	12	B	18.4[86]	0.17[86]	10[92]	**AUC/ C_{max}**	<20[14]
Clavulanic acid	3	125	A	unknown	>100 "freely soluble"	2.5[93]	**AUC/ C_{max}**	>20[14]
Codeine*	1	60	B	>120[94]	>120[94]	3.0-4.0[95]	**AUC/ C_{max}**	>20[14]
Dexketoprofen	1	25	A	0.13[27]	34-63[96]	1.0-1.6[27]	**C_{max}**	20.3, 30.1, 16.5, 12.2[27]
Enalapril*	1	40	Z	>25[17]	>200[17]	2[97]	**C_{max}**	11[98]
Isoniazid*	1	300	B	174[85]	153[85]	2.5-3.5[99]	C_{max}	>20[14]
Lamivudine*	3	300	B	>150[100]	>150[100]	4[101]	**C_{max}**	14.5[16]
Lisinopril	3	20	Z	~100[102]	~100[102]	10[103]	**AUC**	<20
Paracetamol*	1	500	N	20[104]	20[104]	2.0-4.0[33]	**n/a**	n/a
Pentoxifylline	1	400	N	56[105]	42[105]	0.6[106]	**AUC/ C_{max}**	>20[14]
Pravastatin	3	40	A	440[28] or 8[76]	480[28]	2.2[107]	**C_{max}**	12.5[28]
Ranitidine*	3	300	B	>550[108]	>550[108]	4[109]	**C_{max}**	<20[14]
Risperidone	1	6	B	>33[110]	0.97[110]	4[111]	**C_{max}**	13.4, 21.6[30]
Verapamil*	1	240	B	82[20]	11[20]	3.5[112]	**AUC/ C_{max}**	10[113]
Zidovudine*	1	300	N	>18[100]	>18[100]	1.0[114]	**C_{max}**	15.5[18]
Zolpidem	1	10	B	48[29]	6.6[29]	3.2[115]	**C_{max}**	13.7[29]

*biowaiver monograph available[15]

Ionisation type abbreviations: Acid, Base, Neutral, Zwitterion

Table 2 Properties of the 29 BCS 1/3 drugs with no unexpected BE failures

Drug	**BCS class**	**Highest Dose strength**	**Ionisation type**	**Solubility in gastric media pH1.2 (mg/ml)**	**Solubility in Intestinal media pH6.8 (mg/ml)**	**T ½ C_{max} (hr)**
Acyclovir (BCS 1 up to 400mg)	3	400	Z	3.5[116]	2.4[116]	3.8-4.2[117]
Amitriptyline	1	150	B	1000[118]	0.9[118]	7[119]
Amodiaquine	3	153	B	8.6[120]	3.2[120]	4.8[121]
Amoxicillin (BCS 1 up to 875mg)	1	875	Z	7.7[23]	5.4[23]	4[122]
Atenolol	3	100	B	31[123]	25[123]	8[124]
Bisoprolol	1	10	B	795[125]	831[125]	12[126]
Cefalexin	**1**	1000	Z	>17.5[127]	>17.5[127]	2.4[128]
Chloroquine	1	150	B	>100[129]	>100[129]	10[130]
Cimetidine	3	800	B	>1000[131]	18.9[131]	6[132]
Doxycycline	1	200	Z	40[133]	28[133]	14[134]
Ethambutol	3	400	B	771[135]	747[135]	6[136]
Fluconazole	1	200	N	14[137]	6.9[137]	>24[138]
Levetiracetam	1	1000	N	1040[139]	1040[139]	7[140]
Levofloxacin	1	750	Z	200[141]	>30[141]	6[142]
Metformin	3	1000	B	>100[10]	>100[10]	7[143]
Metoclopramide	3	10	B	0.048[144]	0.042[144]	8[145]
Metronidazole	1	500	B	31[25]	12[25]	12[146]
Moxifloxacin	1	400	Z	5[147]	73[147]	10[148]
Ondansetron	1	24	B	47[149]	0.56[149]	6.5[150]
Prednisolone	1	50	N	0.24[151]	0.24[151]	6[152]
Prednisone (BCS 1 up to 20mg)	1	20	N	0.13[24]	0.13[24]	7[153]
Primaquine	1	15	B	8.3[154]	11[154]	8[155]
Proguanil	1	100	B	4.2[156]	2.9[156]	10[157]
Propranolol	1	80	B	56[158]	140[158]	6[159]
Pyrazinamide	3	500	N	23[160]	22[160]	10[161]
Quinidine	1	300	B	9-12[162]	~1.3	12[163]
Quinine	1	300	B	12[164]	1.3[164]	10[165]
Ribavirin	3	600	N	142[166]	142[166]	4.0[167]
Stavudine	1	40	N	>130[100]	>130[100]	2[168]

For each drug in Table 2 a biowaiver monograph is available[15]

Ionisation type abbreviations: Acid, Base, Neutral, Zwitterion

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