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Commentary

The Use of BDDCS in Classifying the Permeability of Marketed Drugs

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Abstract. We recommend that regulatory agencies add the extent of drug metabolism (i.e.,≥90% metabolized) as an alternate method in defining Class 1 marketed drugs suitable for a waiver of *in vivo* studies of bioequivalence. That is,≥90% metabolized is an additional methodology that may be substituted for≥90% absorbed. We propose that the following criteria be used to define≥90% metabolized for marketed drugs: Following a single oral dose to humans, administered at the highest dose strength, mass balance of the Phase 1 oxidative and Phase 2 conjugative drug metabolites in the urine and feces, measured either as unlabeled, radioactive labeled or nonradioactive labeled substances, account for≥90% of the drug dosed. This is the strictest definition for a waiver based on metabolism. For an orally administered drug to be≥90% metabolized by Phase 1 oxidative and Phase 2 conjugative processes, it is obvious that the drug must be absorbed. This proposal, which strictly conforms to the present≥90% criteria, is a suggested modification to facilitate a number of marketed drugs being appropriately assigned to Class 1.

KEY WORDS: BCS; BDDCS; bioequivalence; elimination pathways.

INTRODUCTION

Based on the work of Amidon and colleagues (1) the FDA promulgated the guidance for waiver of *in vivo* bioavailability and bioequivalence testing of immediate-release solid dosage forms for drugs that are Biopharmaceutics Classification System (BCS) Class 1 high-solubility, high-permeability, when such drug products also exhibit rapid dissolution (2). This hallmark guidance reflects the interest of the FDA in decreasing the regulatory burden utilizing a science-led approach.

There is great interest world wide in the BCS and particularly in its use to assure bioequivalence of drug products in developing countries where the infrastructure is usually not available to carry out definitive human bioequivalence studies. The major difficulty in assigning drugs to Class 1, where such drug products would then be amenable to waiver of *in vivo* bioequivalence, is the determination of permeability. In the FDA guidance (2) "a drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of water over a pH range of 1 to 7.5". Such measurements are relatively easy to carry out and in general most investigators agree when classifying drugs as either highly soluble or poorly soluble. However, intestinal permeability is not routinely measured, particularly using methods and laboratory practices that would allow for FDA decision-making, such as *in vivo* biowaiver approval. According to the FDA guidance (2), "In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered highly permeable when the extent of absorption in humans is determined to be equal or greater than 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose". The criteria for data supporting high permeability required by the FDA include 1) human pharmacokinetic studies with information on study design and methods used together with the pharmacokinetic data; 2) direct permeability measurements with supporting data describing the suitability of the study method, the criteria for selection of human subjects, animals or epithelial cell lines, drug concentrations, description of the

Opinions expressed in this report are those of the authors. For those authors affiliated with regulatory agencies (DMB & LXY) the opinions do not necessarily reflect the views or policies of the regulatory agencies.

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ABBREVIATIONS: BCS, Biopharmaceutics Classification System; BDDCS, Biopharmaceutics Drug Disposition Classification System.

Table I. Ability to Correctly Classify BCS Permeability for Estimated CLogP and Log P *vs* Metabolism as Compared to Human Jejunal Permeability Measures Using Metoprolol as the Reference

CLogP	Log P	Extensive vs poor metabolism[a]
19 of 29	19 of 27	27 of 29
65.5%	70.4%	93.1%

[a] Using 70% as the cutoff

analytical method to calculate extent of absorption or permeability, and information on efflux potential; 3) a list of selected model drugs along with data on the extent of absorption in humans used to establish method suitability, permeability values, and class for each model drug, and a plot of extent of absorption as a function of permeability with identification of the low/high permeability class boundary and selected internal standards; or 4) permeability data on the test drug substance, the internal standards, stability information, data supporting passive transport mechanism where appropriate, and methods used to establish high permeability of the test drug substance. Obtaining such information is onerous even for laboratories with expertise in permeability measurement. The scientific community has recognized the need for further regulatory guidance about permeability methodology (3). The factors appear to limit a broad regulatory application of the BCS such that up to now only a limited number of drugs have been accepted by the FDA as Class 1 compounds suitable for a waiver of *in vivo* bioequivalence after strict *in vitro* dissolution criteria have been met.

The permeability studies required to meet the FDA data requirements are exemplified by the human intestinal permeability studies of Lennernäs and coworkers (4–13). In these studies the effective permeabilities of a number of drugs and endogenous substances were determined using regional perfusion of the proximal jejunum in healthy male volunteers. Furthermore, a large number of studies have been carried out attempting to examine the correlation of *in vivo* intestinal permeability measures in rats with those in humans, as reviewed by Cao *et al.* (14).

In 2005, Wu and Benet (15) proposed that a Biopharmaceutics Drug Disposition Classification System (BDDCS) could provide a very simple surrogate for permeability. They suggested that if the major route of elimination for a drug was metabolism, then the drug exhibited high permeability, while if the major route of elimination was renal and biliary excretion of unchanged drug, then that drug should be classified as low permeability. They further proposed that BDDCS may result in a classification system that yields predictability of *in vivo* disposition for all four classes, as well as increasing the number of Class 1 drugs eligible for bioequivalence study waivers. Most recently, Takagi *et al.* (16) compared the BCS and BDDCS classifications using three different permeability reference drugs: metoprolol, cimetidine and atenolol. They reported that the BCS classification using cimetidine as the reference permeability drug appeared to exhibit the best overall agreement with BDDCS, where the agreement in classification of high permeability versus extensive metabolism was approximately 90%. In that 2006 paper, and in a 2004 paper (17), the authors also provided the human jejunal permeability data for 29 of the reference drugs previously studied by Lennernäs, Amidon and coworkers. They evaluated the correlation of these human jejunal permeability experimentally determined values with estimated CLogP and Log P values. Takagi *et al.* (16) and Kasim *et al.* (17), the latter using somewhat different CLogP and Log P values, reported that a plot of the human jejunal permeability against CLogP showed that the classification of permeability based on metoprolol was correct for 19 out of 29 drugs (66%). They noted that 7 of the incorrectly classified drugs (false negatives) are transported by carrier-mediated mechanisms, and two (false positives) are substrates for efflux transporters. A similar plot of the human jejunal permeability against Log P indicated that 70% were correctly classified.

In the present manuscript we further compare BDDCS classification for these 29 reference drugs versus the experimental human jejunal permeability and discuss and make recommendations concerning the use of BCS and BDDCS in reducing the regulatory burden.

Predictions of High and Low Permeability

For the 29 drugs for which measured human permeabilities were available, Table I summarizes the ability to correctly

Table II. Values of CLogP, Log P and Measured Human Permeability for Metoprolol and the 11 Drugs Where Predicted Permeabilities or Extent of Metabolism Did Not Match Measured Permeability Relative to Metoprolol. (Values from Ref. 16)

Drug	CLogP	Predicted permeability	Log P	Predicted permeability	Measured human permeability (x104cm/sec)	Permeability	Metabolism
antipyrine	0.20	L	1.01	L	5.60	H	H
Cephalexin	−1.84	L	−0.67	L	1.56	H	L
d-glucose	−2.21	L	−2.38	L	10.00	H	H
enalapril	0.67	L	1.77	H	1.57	H	H
Furosemide	1.90	H	0.74	L	0.05	L	L
levodopa	−2.82	L	0.00	L	3.40	H	H
l-leucine	−1.67	L	0.34	L	6.20	H	H
Losartan	4.11	H	na		1.15	L	H
Metoprolol	1.49	H	1.72	H	1.34	H	H
Phenylalanine	−1.56	L	0.78	L	4.08	H	H
piroxicam	1.89	H	0.29	L	6.65	H	H
Valacyclovir	−1.22	L	−1.06	L	1.66	H	H

na, not available

classify BCS for estimated CLogP and Log P values versus use of the BDDCS classification of extensive versus poor metabolism. As reported by Takagi *et al.* (16) estimated permeability parameters gave the correct prediction about two thirds of the time. In contrast, as shown in Table I, utilizing the BDDCS definition related to major route of elimination, 27 of 29, or 93% of the drugs' permeabilities were correctly predicted.

Table II lists the 11 drugs where permeability predictions were incorrect together with the values for metoprolol, which was used as the reference. As mentioned above, Takagi *et al.* (16) compared the BCS and BDDCS classifications also using cimetidine and atenolol as reference drugs. Using either cimetidine or atenolol as the reference, the correct BCS classifications for CLogP and Log P would have decreased to 18 of 29 and 18 of 27, respectively, although some differences in drugs would be noted versus those shown in Table II. Of course no change would be found for the predictability of metabolism via BDDCS. In the BDDCS determinations in Tables I and II greater than 70% metabolism was defined as highly metabolized and less than 70% as poorly metabolized.

It should be noted that the human jejunal permeability values are experimental measurements and although Takagi *et al.* (16) and Kasim *et al.* (17) list a single value, coefficients of variation range from 29% for antipyrine to 130% for atenolol as reported by Fagerholm *et al.* (18). The coefficient of variation for metoprolol, the reference drug, was reported to be 60% for a study in 8 healthy volunteers (5, 18). Thus 4 of the 29 drugs, for which human permeability values were listed (16, 17), fall within one standard deviation of the metoprolol value. These 4 drugs are cephalexin, enalapril, losartan and valacyclovir. Note that all 4 of these drugs are listed in Table II where discontinuities between prediction and measured human permeability values are tabulated.

The FDA BCS guidance (2) includes attachment A that lists 20 model drugs suggested for use in establishing suitability of a permeability method. This list is reproduced in Table III with the addition of the accuracy of predictability with CLogP and Log P, and the predictability of metabolism in defining a permeability class. The predicted partition coefficient parameters do not yield the correct permeability for 4 compounds: antipyrine, caffeine, theophylline and furosemide, while the extent of metabolism correctly predicts all 20 model drugs. The FDA lists antipyrine, metoprolol and mannitol as potential Internal Standard (IS) candidates. They also list verapamil as a potential efflux pump substrate (ES) candidate. However, we are unaware of any consistent data that supports the use of verapamil as an efflux pump substrate for intestinal absorption. As noted by Wu and Benet (15) verapamil is a Class 1 drug and its absorption will be unaffected by transporters. It seems unlikely that a good efflux pump substrate would have a human jejunal permeability that is 50% higher than that for antipyrine, as has been reported for both R- and S-verapamil (11). We are not claiming that verapamil is not a good inhibitor of efflux in the intestine nor are we claiming that verapamil is not a substrate for P-glycoprotein in certain cellular systems and in the brain. However, as stated above, we know of no consistent evidence that P-glycoprotein affects verapamil absorption in the intestine. Note that the experimental permeability methods, other than *in vivo* human intestinal absorption measurements, (e.g., Caco-2 permeability assessments) do appear to give the correct prediction when partition coefficients mispredict, as has been shown for theophylline (19), piroxicam (20) and furosemide (21). Likewise, Sahin *et al.* (22) used the Caco-2 cell system to demonstrate that verapamil was not a substrate for intestinal P-gp.

Table III. The 20 Model Drugs Suggested by the FDA for Use in Establishing Suitability of a Permeability Method Together with Predictability Using CLog P and Log P vs Predictability Using Extent of Metabolism

Drug	Permeability class	Predicted by CLogP and Log P	Predicted by extent of metabolism[a]
Antipyrine	High (Potential IS candidate)	No	Yes
Caffeine	High	No	Yes
Carbamazepine	High	Yes	Yes
Fluvastatin	High	Yes	Yes
Ketoprofen	High	Yes	Yes
Metoprolol	High (Potential IS candidate)	Yes	Yes
Naproxen	High	Yes	Yes
Propranolol	High	Yes	Yes
Theophylline	High	No	Yes
Verapamil	High (Potential ES Candidate)	Yes	Yes
Amoxicillin	Low	Yes	Yes
Atenolol	Low	Yes	Yes
Furosemide	Low	No	Yes
Hydrochlorthiazide	Low	Yes	Yes
Mannitol	Low (Potential IS candidate)	Yes	Yes
α-Methyldopa	Low	Yes	Yes
Polyethylene glycol (400)	Low	Yes	Yes
Polyethylene glycol (1000)	Low	Yes	Yes
Polyethylene glycol (4000)	Low (zero permeability marker)	Yes	Yes
Ranitidine	Low	Yes	Yes

[a] Using 70% as the cutoff

PROPOSAL

We recommend that regulatory agencies add the extent of drug metabolism (i.e., ≥90% metabolized) as an alternate method for the extent of drug absorption (i.e.,≥90% absorbed) in defining Class 1 drugs suitable for a waiver of *in vivo* studies of bioequivalence.

We propose that the following criteria be used to define ≥90% metabolized for marketed drugs: Following a single oral dose to humans, administered at the highest dose strength, mass balance of the Phase 1 oxidative and Phase 2 conjugative drug metabolites in the urine and feces, measured either as unlabeled, radioactive labeled or nonradioactive labeled substances, account for ≥90% of the drug dosed. This is the strictest definition for a waiver based on metabolism. For an orally administered drug to be ≥90% metabolized by Phase 1 oxidative and Phase 2 conjugative processes, it is obvious that the drug must be absorbed.

Consensus publications (3, 23, as well as the May 2007 AAPS BE/BCS workshop report to be published) have suggested that the 90% drug absorption criterion is too conservative and an≥85% cut-off is recommended. We agree with this proposed change, (and some authors of this manuscript believe that an even lower percentage for extent of metabolism, such as the 70% used in Table I, II, III, may be appropriate), but here until a regulatory modification is implemented, we propose that the same percentage criteria be adopted for extent of metabolism as holds for extent of absorption. Although others have suggested modifying the FDA dissolution criteria, particularly for acidic drugs (23–26), we continue to support the present BCS dissolution criteria. That is, for biowaiver consideration of the dosage form, the dissolution profile of the test product must be similar to the dissolution profile of the reference product under pH 1.2, 4.5 and 6.8 conditions. We maintain support of the present dissolution requirements, because, as stated above, we believe that permeability agreement is more significant an advancement, and that is our focus here.

Potential upside of such a proposal. The immediate result of this proposal would be that the number of approved drug products eligible for a Class 1 biowaiver of *in vivo* bioequivalence studies would expand markedly. Such a change in the definition of Class 1 compounds would have a marked and significant effect on decreasing the regulatory burden in two ways. First, by the time an approved drug product is eligible for a biowaiver, information concerning the extent of metabolism in humans is readily available and thus classification can be easily accomplished world-wide. Therefore, developing countries can have confidence that *in vitro* dissolution studies can provide assurance that many more drugs and immediate-release drug products can be approved with assurance of product quality. Secondly, in the U.S. and Europe, as well as other developed and developing countries, multiple expensive time consuming human and animal studies are being undertaken to attempt to prove that a particular drug is ≥90% absorbed. These additional expensive studies are not justified, thereby saving both monetary resources and decreasing the number of humans and animals exposed to unnecessary *in vivo* studies. Note, we are not suggesting that companies carry out new mass balance studies for marketed compounds to prove ≥90% metabolism. Rather, we are aware that for many marketed drugs such studies have already been carried out.

Potential downside of such a proposal. Since high solubility is a critical criteria for assignment of a drug as Class 1, the potential downside of the present proposal is that a Class 3 (absorption <90%) drug would be inappropriately designated as Class 1. However, it should be noted that a number of originators of the BCS system, including regulatory scientists, have suggested that Class 3 drugs be eligible for waiver of *in vivo* bioequivalence (23), as proposed by Blume and Schug in 1999 (27). The rationale for Class 3 biowaivers is that permeability controls bioavailability of Class 3 drugs, and thus, solid oral dosage forms of Class 3 drugs that exhibit very rapid dissolution would be expected to show a low risk for inequivalence as their oral solution. Following this thinking the World Health Organization (WHO) has proposed that Class 3 drug products be eligible for a waiver of *in vivo* bioequivalence, thereby increasing the number of drug products that can be approved based only upon *in vitro* dissolution measurement, which would be particularly beneficial to regulatory agencies in developing countries (28). Wu and Benet (15) cautioned that waivers of *in vivo* bioequivalence for Class 3 drugs may be inappropriate "as it is now obvious that components of a Class 3 drug formulation can affect uptake transporters and modify bioavailability." They added, "Until more is known about the importance of intestinal transporters and validated methodology to predict the effects of formulation components on these transporters has been developed, any expansion of *in vivo* bioequivalence study waivers beyond Class 1 compounds is unwise policy." However, even Wu and Benet recognize that when further information is available beyond that known in late 2004, many Class 3 drug products should be eligible for *in vivo* biowaivers considering the specific nontherapeutic (formerly inappropriately designated as "inert") ingredients present in the drug product.

DISCUSSION

Prediction of intestinal drug permeability is a major goal of pharmaceutical scientists. Often in silico methodologies utilize variants of lipid/water partition such as Log P and Clog P as well as other parameters such as log D, polar surface area and hydrogen bonding potential. Table I shows that Log P and Clog P correctly predict high vs low permeability, using metoprolol as the cut off, for approximately 65 to 70% of the "drugs" investigated by Lennernäs, Amidon and co-workers. Takagi *et al.* (16) rationalized the inability of partition parameters to correctly predict the permeability for 9 of the 11 reference drugs in Table II as resulting from transporter effects, which would not be subsumed into an oil/water partition parameter. They also pointed out that there was no evidence for carrier-mediated transport to explain the inaccurate predictions for cephalexin and piroxicam. Two further FDA model drugs, caffeine and theophylline, both having the same structural backbone, yield permeabilities not predicted by partition coefficients (Table III). Yet, the high vs

low permeability for all of the 20 model FDA drugs (Table III) and 27 of 29 of the reference "drugs" listed by Takagi *et al.* (16) are predicted using the extent of metabolism (Table I). It is instructive to note that the two prodrugs investigated, valacyclovir and enalapril, are designed to achieve permeability and then be metabolized and thus are correctly predicted by metabolism but not by partition.

The FDA list of 20 model drugs (Table III) contains 14 drugs in common with those reviewed by Takagi *et al.* (16), thus 35 reference compounds could be evaluated in terms of metabolism predicting permeability. The extent of permeability was correctly predicted for at least 33 of those 35 drugs (94.3%). However, the extent of metabolism may have correctly predicted high vs low permeability for all 35 drugs. Two drugs, cephalexin and losartan, appear to be mischaracterized, as noted in Table II. Note that the partition parameters give the same predictions as metabolism for these two drugs. However, metabolism and partition may have, in fact, correctly predicted that cephalexin is a low permeability drug and that losartan is a high permeability drug. This is due to the fact that the human permeability values tabulated by Takagi *et al.* (16) are point estimates taken from experimental studies. The coefficient of variation for metoprolol permeability in 8 healthy volunteers was 60% (5, 18). The point estimates for the permeabilities of cephalexin and losartan only differ from that of metoprolol by approximately 15%, and one could not conclude that cephalexin has a higher permeability than metoprolol and losartan a lower permeability with any confidence.

The comparisons discussed above used ≥70% metabolism as the definition for extensive metabolism. However, in the present proposal we have taken a more conservative approach and suggested that only marketed drugs documented as ≥90% metabolism be eligible for a waiver of *in vivo* bioequivalence to match the present ≥90% absorption criteria of BCS. Only one of the 35 model compounds in Tables II and III would have its classification changed in setting ≥90% metabolism as the cut-off criteria. That drug is losartan, which already as noted in Table II is on the borderline in terms of *in vivo* intestinal permeability measure correlations.

A minor number of drugs have the potential to be significantly degraded within the gastrointestinal tract (e.g., erythromycin, lansoprazole). Other drugs may be substrates for reductive metabolism by intestinal anaerobic organisms (e.g., digoxin). These three example drugs would not meet the Class 1 solubility criteria, but to address the concern about degradation/metabolism within the gut lumen, we have limited the metabolism to Phase 1 oxidative and Phase 2 conjugative metabolites. Other potential concerns for drugs that are biliary cycled or exhibit saturable metabolism should not be relevant since the criteria is based on mass balance of Phase 1 and Phase 2 metabolites in urine and feces. The present guidance (2) restricts BCS-based biowaivers for narrow therapeutic range drugs. This seems more related to a risk analysis of the potential consequences of bioinequivalence than a genuine scientific concern about assuring bioequivalence.

Because metabolites can be excreted in the bile, it is not possible to only use urinary excretion values to validate the extent of metabolism. However, we do note that using values for percent excreted unchanged obtained from the pharmacokinetic compilation in Goodman and Gilman, many Class 1 and Class 2 drugs should be shown to be ≥90% metabolized. For 40 Class 2 drugs listed by Wu and Benet (15), the average percent excreted unchanged±S.D. was 3.2±4.0%, and for 47 Class 1 drugs the values were 9.5±11.9%.

One of the most intriguing aspects of the finding that the extent of metabolism does such an excellent job in predicting intestinal permeability is the recognition of the apparent commonality of permeability characteristics of the intestine and the liver following oral drug dosing. Both organs have significant metabolic capabilities and it is now recognized that both contain uptake and efflux transporters that affect drug disposition. It is only recently that it has been universally recognized that major metabolic elimination of a drug can occur in the intestine following oral dosing (29). However, for an orally administered drug to be extensively metabolized, that drug must have been absorbed.

We recognize that other in silico methods beyond the discussed correlations with Log P and CLogP presented by Takagi *et al.* (16) will potentially provide better predictions of High Permeability/Extensive Metabolism versus Low Permeability/Poor Metabolism, e.g. Winiwarter *et al.* (30). However, that is not the purpose of the present manuscript, which is rather to provide an easier method of determining Class 1 assignment for marketed drugs.

Finally, the extensive metabolism proposal presented here is suggested as an alternate (additional) method for assigning Class 1 drugs beyond ≥90% absorption. We recognize that certain poorly metabolized drugs, such as sotolol, can be shown to exhibit ≥90% and be approved by the FDA as a Class 1 drug. Although the names of many of the drugs designated by the FDA are proprietary, we suspect that sotolol is not the only poorly metabolized drug on the list (which probably includes drugs from the classes of cephalosporins and quinolones). Whether or not the ≥90% absorption of sotolol (and the potential other drugs that are not metabolized) is a result of uptake transporters, as would be predicted by Wu and Benet (15), is a subject for future studies. However, we emphasize again that the proposal here, which is a suggested modification to facilitate a significant number of marketed drugs being appropriately assigned to Class 1, only suggests that metabolism be added to (not substituted for) the present BCS requirement.

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