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The FDA Should Eliminate the Ambiguities in the Current BCS Biowaiver Guidance and Make Public the Drugs for which BCS Biowaivers Have Been Granted

L. Z. Benet¹ and C. A. Larregieu¹

¹Department of Bioengineering and Therapeutic Sciences, Schools of Pharmacy and Medicine, University of California San Francisco, San Francisco, CA 94143-0912

Abstract

Although FDA approved BCS Class 1 drugs are designated as high permeability, in fact, the criterion utilized is high extent of absorption. This ambiguity should be eliminated and the FDA criterion should explicitly be stated as 90% absorption based on absolute bioavailability or mass balance. Maintaining confidentiality of the drugs for which the FDA has approved BCS waivers of *in vivo* bioequivalence studies is not good public policy and should be reversed.

Keywords

Biopharmaceutics Classification System; BCS; FDA; intestinal permeability; extent of absorption

Introduction

The FDA Biopharmaceutics Classification System (BCS) (1, 2) was developed to predict *in vivo* absorption performance of drugs from measurements of solubility and intestinal permeability. This was based on the BCS analysis stating (2) that “one would expect to obtain a good correlation between extent of absorption and intestinal membrane permeability for high solubility drugs...”. The FDA has since based their criterion for permeability on the extent of absorption of a drug. We believe using the extent of absorption (a thermodynamic measure) and intestinal permeability (a kinetic measure) interchangeably is not scientifically sound and is ambiguous from a regulatory perspective. It appears that the FDA is maintaining the ambiguous “high permeability” criterion for historical reasons although an unambiguous criterion “high extent of absorption” is, in fact, utilized by the Agency in the great majority of recent, if not all, BCS Class 1 assignments. The 2010 EMA “Guideline on the Investigation of Bioequivalence” only allows *in vivo* biowaivers based on the extent of absorption (3). We see no advantage in regulatory agencies continuing to utilize an ambiguous criterion when an unambiguous criterion is available. As a result, the FDA criteria for BCS waiver of *in vivo* bioequivalence studies should be based on extent of absorption, not intestinal permeability.

To whom correspondence should be addressed. leslie.benet@ucsf.edu. Mailing Address: Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, 533 Parnassus Ave., Room U-68, San Francisco, CA 94143-0912. Tel: 415-476-3853. Fax: 415-476-8887.

Only a relatively small number of drugs (we estimate 20–25) have received FDA certifications as Class 1 drugs for which the agency will allow a waiver of *in vivo* bioequivalence studies and approve bioequivalence for immediate release products based on a rapid dissolution criteria. The uncertainty concerning the number of drugs eligible for a biowaiver results from the FDA's decision that approval to market a drug product resulting from submission of biowaiver requests is entitled to confidentiality. We believe that this is bad public policy and should be reversed, since such a policy is contrary to the US Federal government's support of regulations that lead to an overall decrease in costs when no safety or efficacy concerns are a consequence of the cost savings. We believe that companies should continue to be required to submit data to the FDA supporting the use of an *in vivo* bioequivalence study waiver together with appropriate dissolution data. However, when waivers are granted this information should be made public just as an approval of a generic equivalent product based on an *in vivo* bioequivalence study is made public. We further believe that the public has the right to know when the FDA is approving new or reformulated drug products based only on dissolution studies rather than *in vivo* bioequivalence studies. The advantage to the pharmaceutical industry, the US public and particularly to regulatory agencies in developing countries is that when such information is made public it will be recognized that for a particular drug a sponsor has been able to provide acceptable scientific data to a regulatory agency justifying a waiver of bioequivalence.

Intestinal Permeability vs. Extent of Drug Absorption

The ambiguity of the regulatory/scientific issues of intestinal permeability and the extent of absorption may be traced back to the initial theoretical basis proposed by Amidon *et al.* for the BCS (2). In that paper, the authors demonstrated a good correlation between measured human intestinal jejunal permeability and the extent of absorption for 25 drugs and 4 nondrugs. We have no argument with the outcome of this excellent seminal work, which suggested that for highly soluble drugs, high intestinal permeability will result in a good extent of absorption. However, even in this earliest presentation by Amidon *et al.* (2) the authors overstep basic physical chemical principles by stating "Based on the above analysis, one would expect to obtain a good correlation between extent of absorption and intestinal membrane permeability for high solubility drugs that are dosed in solution or for high solubility drugs in dosage forms that dissolve very rapidly." Here the authors are suggesting that drugs exhibiting poor human intestinal jejunal permeability will exhibit a poor extent of drug absorption. In fact, the authors did not have sufficient data to support either of the conclusions (i.e. high permeability results in high extent of absorption or low permeability results in poor extent of absorption) that could potentially violate the recognized lack of predictability of kinetics for thermodynamics and thermodynamics for kinetics.

The FDA Uses the Extent of Absorption and Permeability Interchangeably

We believe that current implementation by the FDA of the Biopharmaceutics Classification System (BCS) for drugs in which the *in vitro* dissolution criteria of the drug product may be substituted for an *in vivo* bioequivalence study inappropriately uses the extent of absorption and intestinal permeability interchangeably. A recent publication by FDA scientists Chen

and Yu (4), we believe, confirm the Agency's use of these kinetic and thermodynamic parameters interchangeably.

The FDA Guidance (1) states that "The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane". However, a further statement in the same paragraph as the quote above reads, "...a drug substance is considered to be *highly permeable* when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose" (emphasis added by FDA). We further note that the discussion of the BCS Guidance on the FDA website only contains this 90% statement under the heading Class Boundaries (5). In this FDA summary there are two headings under Permeability Determination. The first is "Extent of absorption in humans" followed by two bulleted methods: "Mass-balance pharmacokinetic studies" and "Absolute bioavailability studies". This is followed by the listing of four intestinal permeability methods. In Table 2 of Chen and Yu (4), titled, "Drugs with High Intestinal Permeability and Poor Metabolism", high permeability for all 14 drugs is justified based on mass balance measurements (absolute bioavailability or amount of drug excreted unchanged in the urine). There are no human intestinal permeability measures for any of these drugs. But, for three of the 14 drugs, (levofloxacin, ofloxacin and sotalol) *in vitro* permeation studies using Caco-2 cells vs. metoprolol are available and referenced by Chen and Yu (4). All three of these drugs' permeabilities, at their highest dose strength concentration in 250 ml of water, are less than that of metoprolol. In questioning the FDA as to why levofloxacin and ofloxacin are classified by Volpe (6) as high permeability based on Caco-2 measurements, the following response was given: "Although the FDA BCS guidance has identified metoprolol as a potential high permeability internal standard, firms proposed to use labetalol as a high permeability internal standard, which was accepted by the FDA. As such, the FDA has classified drugs whose Caco-2 permeabilities are higher than labetalol's, but lower than metoprolol's, as high permeability drugs". We accept this explanation, although no confirming human *in vivo* permeability measurements for labetalol have been published. There is no doubt that the Caco-2 permeability of sotalol is 4% of metoprolol and 7% of labetalol as determined by Yu and FDA coworkers (7). Here the FDA's explanation is that "FDA's policy is that *in vivo* human data triumph over any animal and/or *in vitro* data". Since human permeability measures are available for none of the 14 drugs listed by Chen and Yu (4) as high permeability and only 3 had Caco-2 measures, we don't see how it can be argued that the FDA is not using extent measures as a surrogate for permeability. A further statement found in the Guidance (1) reads: "High permeability assures that absorption is not limited by permeability, and thus drug absorption is complete". Here again, in our opinion, the FDA has inappropriately redefined high permeability not as a kinetic measure but rather in terms of not limiting extent of absorption. We believe there is ample evidence that the FDA frequently uses the extent of absorption and permeability interchangeably, which is the reason we are writing this paper and advocating that this not be done by the FDA.

It May be Justified for Regulatory Agencies to Use Surrogate Measures as the Basis for Classifying a Drug as 90% Absorbed

The human permeability studies of 30 drugs and 4 nondrugs by Amidon, Lennernas, and co-workers (2, 8) for the most part showed that the predictability of highly absorbed compounds is consistently correlated with a human *in vivo* intestinal jejunal permeability equal to or greater than metoprolol. Thus, regulatory agencies may choose to accept high permeability measures as a surrogate for high extent of absorption. However, as noted above, the Agency has been reluctant to do this since so few drugs have been accepted by the FDA as fulfilling their Class 1 criteria. A second surrogate for a high extent of absorption could be a high extent of metabolism as proposed by Benet *et al.* (9). These investigators recommended that regulatory agencies add the extent of drug metabolism (i.e.,

90% metabolized) as an alternative method for the extent of drug absorption (i.e., greater than or equal to 90% absorbed) in defining Class 1 drugs suitable for a waiver of *in vivo* studies of bioequivalence. They proposed 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 non-radioactive 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." It should be noted that the 2010 EMA Guideline has accepted these metabolism measures as a basis for an *in vivo* bioequivalence study biowaiver (3). Mass balance studies have been recently reviewed (10).

The BCS guidance does allow the possibility that biowaivers may be based on *in vitro* measures, which would be very useful for regulatory agencies in developing countries. In its guidance for industry (1), the FDA recommends that if an alternative method to human extent of absorption/permeability is utilized, a list of 20 model drugs are suggested to be used in establishing the suitability of an alternative method. The most commonly employed alternate approach is the use of permeability measurements through the human colon carcinoma cell line, Caco-2. Countless studies have been carried out and published in the literature reporting permeability measurements for this cell line. However, we suspect that such measures have only served as the basis for at most 1 or 2 FDA BCS Class 1 designations, and possibly none, unless confirmatory *in vivo* absorption data is available. Since the FDA has ruled that such information is confidential, we cannot know if any drugs have been approved only on the basis of *in vitro* permeability measures. We question the reliability of biowaivers based only on *in vitro* measures (11), but will address this in a further manuscript.

Confidentiality of Information Concerning BCS Class 1 Biowaivers Should Be Rescinded

We can only speculate as to the basis for the FDA decision to maintain confidentiality on drug products that have been approved subject to a biowaiver of *in vivo* bioequivalence.

However, whatever the reason, we strongly disagree with this confidentiality. Just as the public has the right to know if a generic drug product is approved based on an *in vivo* bioequivalence test in lieu of efficacy and safety studies (an AB rated product in the Orange Book), we believe the public has the right to know if a marketed product has been approved based on a BCS Class I biowaiver, and a new ABW designation should be introduced for such products.

Conclusions

1. It is not good regulatory practice to continue to support an ambiguous criterion (intestinal permeability) for a biowaiver of *in vivo* bioequivalence studies, when an unambiguous criterion is available. The unambiguous criterion is 90% absorbed and it should supersede all permeability measures, both *in vivo* and *in vitro*. The FDA should follow the EMA and explicitly indicate that extent of absorption in humans based on absolute bioavailability or mass balance should be the basis for a biowaiver of *in vivo* bioequivalence studies.
2. Mass balance determined by including measures of Phase 1 and Phase 2 metabolites, as proposed by Benet *et al.* (9) and as now accepted by EMA (3), should also be accepted as a basis for extent of absorption calculations.
3. Confidentiality of the drugs approved by the FDA for a BCS biowaiver should be eliminated and drug products approved on the basis of a BCS biowaiver should be so listed in the Orange Book with an ABW rating.

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