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Commentary

Biopharmaceutics Classification System: The Scientific Basis for Biowaiver Extensions[1]

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INTRODUCTION

Since the introduction of the Biopharmaceutics Classification System (BCS) (1), its validity and applicability have been the subject of extensive research and discussion (2). These efforts have resulted in an improved SUPAC-IR guidance (3), a dissolution guidance (4), and a Food and Drug Administration (FDA) guidance on waiver of *in vivo* bioequivalence studies for BCS Class I drugs in rapid dissolution immediate-release (IR) solid oral-dosage forms (5). The BCS guidance generally is considered to be conservative with respect to the class boundaries of solubility and permeability in addition to the dissolution criteria. Thus, the possibility modifying these boundaries and criteria to allow waivers of *in vivo* bioequivalence studies "biowaivers" for additional drug products has received increasing attention (6). In this commentary, we present a discussion of the relevant scientific issues that have been or will be examined when extensions of biowaivers to additional IR solid oral drug products are considered. It is hoped that this commentary will stimulate more discussion in the scientific community and ultimately result in new regulatory policies.

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability (1). When combined with the *in vitro* dissolution characteristics of the drug product, the BCS takes into account three major factors: solubility, intestinal permeability, and dissolution rate, all of which govern the rate and extent of oral drug absorption from IR solid oral-dosage forms (5).

The solubility classification of a drug in the BCS is based on the highest dose strength in an IR product. A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media over the pH range of 1.0–7.5; otherwise, the drug substance is considered poorly soluble. The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe the administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.

The permeability classification is based directly on the extent of intestinal absorption of a drug substance in humans or indirectly on the measurements of the rate of mass transfer across the human intestinal membrane. Animal or *in vitro* models capable of predicting the extent of intestinal absorption in humans may be used as alternatives, e.g., *in situ* rat perfusion models and *in vitro* epithelial cell culture models. A drug substance is considered highly permeable when the extent of intestinal absorption is determined to be 90% or higher. Otherwise, the drug substance is considered to be poorly permeable.

An IR drug product is characterized as a rapid-dissolution product when not less than 85% of the labeled amount of the drug substance dissolves within 30 min using USP Apparatus I at 100 rpm or USP Apparatus II at 50 rpm in a volume of 900 mL or less of each of the following media: 1) acidic media, such as 0.1 N HCl or USP simulated gastric fluid without enzymes; 2) a pH 4.5 buffer; and 3) a pH 6.8 buffer or USP simulated intestinal fluid without enzymes. Otherwise, the drug product is considered to be a slow dissolution product.

FDA GUIDANCE ON BIOWAIVERS

The FDA issued a guidance for industry on waivers of *in vivo* bioavailability and bioequivalence studies for IR solid oral-dosage forms based on the BCS in August 2000 (5). This BCS guidance recommends that sponsors may request biowaivers for highly soluble and highly permeable drug sub-

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stances (Class I) in IR solid oral-dosage forms that exhibit rapid *in vitro* dissolution, provided the following conditions are met: 1) the drug must be stable in the gastrointestinal tract; 2) excipients used in the IR solid oral-dosage forms have no significant effect on the rate and extent of oral drug absorption; 3) the drug must not have a narrow therapeutic index; and 4) the product is designed not to be absorbed in the oral cavity.

Based on the scientific principles of the BCS, observed *in vivo* differences in the rate and extent of absorption of a drug from two pharmaceutically equivalent solid oral products may be due to *in vivo* differences in drug dissolution. When the *in vivo* dissolution of an IR oral dosage form is rapid in relation to gastric emptying, the rate and extent of drug absorption is likely to be independent of drug dissolution. Therefore, similar to oral solutions, demonstration of *in vivo* bioequivalence may not be necessary as long as the inactive ingredients used in the dosage form do not significantly affect the absorption of the active ingredient. Thus, for BCS Class I (high solubility-high permeability) drug substances, demonstration of rapid *in vitro* dissolution using the recommended test methods would provide sufficient assurance of rapid *in vivo* dissolution, thereby ensuring human *in vivo* bioequivalence. In our opinion, the potential benefit of this FDA guidance is not only lowering expenditures associated with bioavailability/bioequivalence studies but more critically expediting the development of new chemical entities for the marketplace, entities that will ultimately be of benefit to the health of the American public.

BIOWAIVER EXTENSION POTENTIAL

Potential of Redefining BCS Solubility Class Boundary

The solubility class boundary requires that the highest strength of a drug substance is soluble in 250 mL or less of aqueous media over the pH range of 1.0–7.5. The pH range of 1.0–7.5 for solubility studies is a stringent requirement and may not be necessary. Under fasting conditions, the pH range in the GI tract vary from 1.4 to 2.1 in the stomach, 4.9 to 6.4 in the duodenum, 4.4 to 6.6 in the jejunum, and 6.5 to 7.4 in the ileum (9). Furthermore, it generally takes approximately 85 min for a drug to reach the ileum (8). By the time the drug reaches the ileum, the dissolution of the drug product is likely complete if it meets the rapid dissolution criterion, i.e., no less than 85% dissolved within 30 min. Therefore, it would appear reasonable to redefine the pH range for BCS solubility class boundary from 1.0–7.5 to 1.0–6.8 in alignment with dissolution pH ranges, which are pH 1.0, 4.5, and 6.8 buffers.

The dose volume of 250 mL seems a conservative estimate of what actually is available *in vivo* for solubilization and dissolution. The physiological volume of the small intestine varies from 50 to 1100 mL with an average of 500 mL under the fasted conditions (10). When administered with a glass of water, the drug is immersed in approximately 250 mL of liquid in the stomach. If the drug is not in solution in the stomach, gastric emptying would then expose it to the small intestine, and the solid drug would dissolve under the effect of additional small intestinal fluid. However, because of the large variability of the small intestinal volume, an appropriate definition of the volume for solubility class boundary would be difficult to set.

Another factor influencing *in vivo* solubility is bile salt/micelle solubilization (11). Intestinal solubility is perhaps the most important solubility because this is the absorbing region for most drugs. Many acidic drugs whose solubility is low at low pH are well absorbed. For example, most nonsteroidal anti-inflammatory drugs, such as flurbiprofen, ketoprofen, naproxen, and oxaprozin, are poorly soluble in the stomach but are highly soluble in the distal intestine and their absolute human bioavailabilities are 90% or higher, thus exhibiting behavior similar to those of BCS Class I drugs (7).

The solubility classification is based on the ability of a drug to dissolve in plain aqueous buffers. However, bile salts are present in the small intestine, even in the fasted state. The average bile salt concentration in the small intestine is estimated to be approximately 5 mM (9). Based on physiological factors, Dressman designed two kinds of media, one to simulate the fasted-state conditions in the small intestine and the other to simulate the fed-state conditions in the small intestine (9). These two media may be used in drug discovery and development processes to assess *in vivo* solubility and dissolution and have the potential to be used in drug regulation, i.e., dissolution methodology for bioequivalence demonstration using more physiologically relevant media, although more extensive research is needed.

Other criteria, such as intrinsic dissolution rate, may be useful in the classification of the biopharmaceutic properties of drugs. The intrinsic dissolution method has been widely used in pharmaceutical industries to characterize drug substances. Our recent data have shown that the intrinsic dissolution method is robust and easily determined. A good correlation between the intrinsic dissolution rate and BCS solubility classification was found for 17 BCS model drugs (12). Thus, the intrinsic dissolution rate may be used when the solubility of a drug cannot be accurately determined, although more validation research needs to be conducted.

Potential of Redefining BCS Permeability Class Boundary

The permeability class boundary is based on the extent of intestinal absorption (fraction of dose absorbed) of a drug substance in humans or on measurements of the rate of mass transfer across intestinal membranes. Under the current BCS classification, a drug is considered to be highly permeable when the fraction of dose absorbed is equal to or greater than 90%. The criterion of 90% for the fraction of dose absorbed can be considered conservative because the experimentally determined fraction of dose absorbed is seen to be less than 90% for many drugs that are generally considered completely or well-absorbed. This suggests that a class boundary of 85% might be appropriate in defining high permeability, although it remains to be justified and debated.

Biowaiver Extension Potential to BCS Class II Drugs

BCS Class II drugs exhibit low solubility and high permeability characteristics. The scientific rationale for granting biowaiver extension for Class II drugs is that their oral absorption is most likely limited by *in vivo* dissolution. If *in vivo* dissolution can be estimated *in vitro*, it is possible to establish an *in vitro-in vivo* correlation. *In vitro* dissolution methods that mimic *in vivo* dissolution methods for Class II drugs are appealing, but experimental methods can be difficult to de-

sign and to validate because of the numerous *in vivo* processes involved (9). Further, the intestinal absorption of Class II drugs can be limited by its solubility (13). The key determinant then is the solubility in the absorbing region of the intestine. The solubilization can be affected by pH and/or surfactants in this region. This suggests a potential to define an intermediate solubility class for drugs that are soluble either in the intestine or in the stomach.

The dissolution of formulations containing poorly soluble drugs may require an addition of sodium lauryl sulfate or other surfactants to mimic the solubilization *in vivo* and the maintenance of sink conditions *in vivo* resulting from continuous absorption. For example, the recommended USP dissolution media for medroxyprogesterone acetate tablet, danazol capsule, carbamazepine tablet, and flutamide tablet contain 0.5%, 0.75%, 1%, and 2% SLS, respectively (USP 24-NF19, 2001). Although the dissolution medium with various surfactant concentrations may be adequate for the purpose of product quality control, this is clearly not sufficient for predicting *in vivo* dissolution. There is a need to do more research to develop uniform dissolution media reflecting *in vivo* dissolution conditions.

For BCS Class II drugs, excipients can, in principle, affect both solubility and permeability. Some BCS Class II drugs, such as HIV protease inhibitor amprenavir, require specific formulation effort to enhance their solubility and permeability (14). An excipient effect on solubility can be investigated *in vitro* and *ex vivo*, and more research of this type is underway.

Biowaiver Extension Potential to BCS Class III Drugs

Drugs with high solubility and low permeability are classified as BCS Class III drugs. It has been suggested that biowaivers be extended to BCS Class III drugs with rapid dissolution property. It has been contended that there are equally compelling reasons to grant biowaivers to Class III drugs as there are for Class I drugs (6).

Scientific Rationale

The absorption of a Class III drug is likely limited by its permeability and less dependent upon its formulation, and its bioavailability may be determined by its *in vivo* permeability pattern (6,15). If the dissolution of Class III products is rapid under all physiological pH conditions, it can be expected that they will behave like an oral solution *in vivo*. *In vivo* bioequivalence studies generally are waived for oral solution drug products because the release of the drug from an oral solution is self-evident (16).

Nevertheless, the absorption kinetics from the small intestine are influenced by a combination of physiological factors and biopharmaceutical properties such as gastrointestinal motility, permeability, metabolism, dissolution, and the interaction/binding of drugs with excipients (18,19). A recent survey of the FDA data of over 10 BCS Class III drugs shows that most commonly used excipients in solid dosage forms have no significant effect on absorption. If the excipients used in two pharmaceutically equivalent solid oral IR products do not affect drug absorption and the two products dissolve very rapidly in all physiologically relevant pH ranges (i.e., > 85% in 15 min), there would appear to be no reason to believe that these two products would not be bioequivalent.

Potential Excipient Effect on Motility and Permeability

Because Class III compounds often exhibit site-dependent absorption properties (17,18), the transit time through specific regions of the upper intestine may be critical for bioequivalence, suggesting a more stringent dissolution criterion to ensure complete dissolution in the stomach. Certain excipients have been shown to influence gastrointestinal transit time. For example, scintigraphy has indicated that sodium acid pyrophosphate could reduce the small intestinal transit time by as much as 43% compared to controls (19). Poorly absorbed sugar alcohols, such as sorbitol and mannitol, can also decrease small intestinal transit time (20). Therefore, Class III oral drug products containing a significant amount of transit-influencing excipients should be excluded from consideration of biowaivers. Although most commonly used excipients in solid dosage forms are unlikely to influence the gastrointestinal transit time significantly, the evidence by no means is conclusive.

The effects of excipients on permeability have been reviewed in the literature (21). Excipients that can significantly affect permeability *in vitro* include surfactants, fatty acids, medium-chain glycerides, steroidal detergents, acyl carnitine and alkanoylcholines, *N*-acetylated non-α amino acids, chitosans, and other mucoadhesive polymers. Rege *et al.* (22) investigated the effect of some formulation excipients on Caco-2 permeability and found that several commonly used IR formulation excipients did not modulate drug permeability across Caco-2 monolayers.

Dissolution

In vivo dissolution plays a more important role for Class III IR drug products than it does for Class I drug products. Dissolution tests with USP Apparatus I at 100 rpm (or USP Apparatus II at 50 rpm) in a volume of 900 mL of various pH media are recommended in the FDA guidance to evaluate the product dissolution *in vitro*. For highly soluble and highly permeable drugs, rapid dissolution *in vitro* (no less than 85% in 30 min) can most likely ensure rapid *in vivo* dissolution. However, the demonstration of rapid *in vitro* dissolution of Class III drug products may not ensure rapid dissolution *in vivo* simply because sink conditions may not exist under *in vivo* conditions. To minimize the possibility of dissolution behavior anomalies, it was found in our simulation studies that it would be necessary to set a more rapid *in vitro* dissolution rate criterion of no less than 85% within 15 min for Class III drugs (23).

Transporters

Numerous *in vitro* Caco-2 studies have suggested that transporters may enhance or limit the absorption of many drugs such as digoxin and HIV protease inhibitors, including indinavir, ritonavir, and saquinavir (15,24). On the other hand, many transporter substrates show complete intestinal absorption and dose proportionality *in vivo*, implying that transporters do not significantly influence *in vivo* absorption. This apparent discrepancy between *in vitro* and *in vivo* behavior may be explained by the potential inherent differ-

ences in the two systems as well as by the experimental conditions adopted in the comparisons. For example, a new chemical entity was found to be a strong P-glycoprotein substrate and was classified as a low permeability compound based on *in vitro* Caco-2 studies. However, its absolute bioavailability in humans was greater than 90%, and dose proportionality was demonstrated over a 60-fold dose range. The concentration of the compound in the *in vitro* Caco-2 studies was approximately 3400-fold lower than the estimated concentration *in vivo*, which may account for the large discrepancy between the *in vivo* and the *in vitro* findings of its permeability characteristics. Thus, *in vitro* studies must be extrapolated to *in vivo* with great care. Nevertheless, the potential impact of transporters on absorption should be thoroughly investigated and understood when considering biowaiver extensions.

Intermediate Permeability Classification

In general, the lower the permeability of a Class III drug, the more significant the effect of excipients on absorption and the higher the likelihood of bioinequivalence. Therefore, it has been proposed to define an intermediate permeability class so that drugs with 89% fraction of dose absorbed would not be treated the same as drugs with 1% fraction of dose absorbed. However, how to define the intermediate permeability class remains to be addressed.

SUMMARY

The current BSC guidance issued by the FDA allows for biowaivers based on conservative criteria. Possible new criteria and class boundaries are proposed for additional biowaivers based on the underlying physiology of the gastrointestinal tract. The proposed changes in new class boundaries for solubility and permeability are as follows:

1. Narrow the required solubility pH range from 1.0–7.5 to 1.0–6.8.
2. Reduce the high permeability requirement from 90% to 85%.

The following new criterion and potential biowaiver extension require more research:

1. Define a new intermediate permeability class boundary.
2. Allow biowaivers for highly soluble and intermediately permeable drugs in IR solid oral dosage forms with no less than 85% dissolved in 15 min in all physiologically relevant dissolution media, provided these IR products contain only known excipients that do not affect the oral drug absorption.

The following areas require more extensive research:

1. Increase the dose volume for solubility classification to 500 mL.
2. Include bile salt in the solubility measurement.
3. Use the intrinsic dissolution method for solubility classification.
4. Define an intermediate solubility class for BCS Class II drugs.
5. Include surfactants in *in vitro* dissolution testing.

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