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Commentary

G.L. Amidon, H. Lennernas, V.P. Shah, and J.R. Crison. *A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability*, Pharm Res 12, 413–420, 1995—Backstory of BCS

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Abstract. The Biopharmaceutics Classification System (BCS) has become widely accepted today in the academic, industrial, and regulatory world. While the initial application of the BCS was to regulatory science bioequivalence (BE) issues and related implications, it has come to be utilized widely by the pharmaceutical industry in drug discovery and development as well. This brief manuscript will relate the story of the BCS development. While much of the ground work for the BCS goes back to the pharmacokinetic and drug absorption research by Gordon Amidon (GLA) in the 1970s and 1980s, the realization of the need for a classification or categorization of drug and drug products for setting dissolution standards became apparent to GLA during his 1990–1991 sabbatical year at the FDA. Initiated at the invitation of the then CEDR director, Dr. Carl Peck, to become a visiting scientist at the FDA, the goal was to promote regulatory research at the FDA, in my case, in biopharmaceutics, and to develop a science-based system to simplify regulatory requirements.

KEY WORDS: absorption; biopharmaceutics; dissolution standards; intestinal permeability; solubility.

INTRODUCTION

The Biopharmaceutics Classification System (BCS) has become widely accepted today in the academic, industrial, and regulatory world. While the initial application of the BCS was to regulatory science bioequivalence (BE) issues and related implications, it has come to be utilized widely by the pharmaceutical industry in drug discovery and development as well. This brief manuscript will relate the story of the BCS development. While much of the ground work for the BCS goes back to the pharmacokinetic and drug absorption research by Gordon Amidon (GLA) in the 1970s and 1980s, the realization of the need for a classification or categorization of drug and drug products for setting dissolution standards became apparent to GLA during his 1990–1991 sabbatical year at the FDA. Initiated at the invitation of the then CEDR director, Dr. Carl Peck, to become a visiting scientist at the FDA, the goal was to promote regulatory research at the FDA, in biopharmaceutics, and to develop a science-based system to simplify regulatory requirements.

GLA began working with Drs. Vinod Shah and Jerome Skelly in the FDA Division of Biopharmaceutics, in 1990, on the problems of and regulatory standards for drug product dissolution. In reviewing drug product dissolution standards, it became clear that some drug products were simple while other drug products were complex, suggesting that some type of categorization or classification would be useful for setting regulatory standards. That is, simple standards for simple drug products and complex standards for complex drug products. Initially, it was not obvious where to start with such a classification, though the need and potential utility was clear. A clear starting point would require a sound, well-established scientific principle as a starting point for classification and it would be critical that the principle be well accepted by the scientific community. Where to start and how to build such a classification occupied much of the thinking over the 1990–1992 time period.

A deeper question was the use of dissolution testing in the regulation of oral drug products. Dissolution testing has been extensively developed and used as a critical quality control (QC) specification for oral drug products. The use of dissolution as a component of the bioequivalence (BE) standard, though clearly recognized as important, was less well developed and less discussed by the scientific community.

By 1990, GLA had developed methods for predicting absorption in humans utilizing animal intestinal jejunal permeabilities (1) for soluble drugs (2), and separated the absorption (fraction absorbed, F_{abs}) and metabolism components of systemic availability (F_{sys}) and was extending the absorption prediction approaches to insoluble drugs (3). The absorption prediction methods clearly established the intestinal membrane permeability (P_{eff}) as a key variable in human absorption prediction (2,4,5).

As is often the case in science, parallel developments play a catalyzing role in advancing science; in this case,

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Dr. Hans Lennernas, then a graduate student of Dr. Lennart Paalzow at the University of Uppsala, adapted and developed an intubation technique, the Loc-I-Gut®, for determining intestinal permeability in humans (6–8), utilizing the methods we had developed for animals (1,4). The availability of human data, in this case, intestinal permeabilities, was crucial, in my mind, for making any type of regulatory advance. Further, the availability of a human database would be "gold" standard for absorption prediction (2).

The BCS approach to classifying drug and drug products crystallized during the 1991–1992 time period. Methods were developed for predicting fraction absorbed (F_{abs}) for soluble drugs and work was in progress to predict absorption of insoluble drugs (2,3,9). It became clear that Fick's first law applied to a membrane, where drug partitioned into a membrane, and where permeability replaced the diffusivity of Fick's first law was the scientific conceptual starting point for a classification. The intestinal membrane permeability was a boundary condition on the differential equations for predicting absorption (1), while the drug solubility was the upper limit to drug concentration at the membrane aqueous interface. Thus, the equation or, actually, the boundary condition to the above noted transport equations

$$J_{max} = (1/A)dM/dt = P_{eff} \times C_s \quad \text{(Eq.1.)}$$

became the scientific basis for the BCS approach. In Eq. 1, the flux (J) is the mass (M) per unit area (A) absorbed in to the membrane per unit time (t) and is determined by the product of the local membrane permeability (P_{eff}) and the concentration (C) at the membrane luminal fluid interface, with the maximum concentration being the solubility (C_s). This suggested a strong scientific basis for the permeability–solubility classification system. While the complexity of the intestinal membrane permeability (P_{eff}) and the solubility (C_s) in the gastrointestinal track was well recognized at the time of the original publication and the draft FDA guidance, the permeability and solubility would be a pivotal starting point for BCS classification.

Thus, based on mass transport analysis of the gastrointestinal tract, the BCS classification system was proposed to the FDA. The critical need for development and particularly, for the regulatory use of the BCS was human data; *i.e.*, human permeabilities with which to support a regulatory standard or guidance.

Thus, Hans Lennernas and GLA convinced the FDA and the Swedish Medicine Products Agency (MPA) to fund a study to determine human jejunal permeabilities with the former's newly developed "Loc-I-Gut" technique (6,8) and evaluate the basis for a Biopharmaceutics Classification System (BCS). Dr. Larry Lesko of the FDA managed the permeability studies that were conducted at Uppsala University and the University of Michigan to determine drug permeabilities of three selected drugs in each BCS class.

The BCS approach continued to evolve over several years under the FDA research contract with Gordon and Hans as PI's and Vinod as the project officer. The goal of this research was to develop a sound science-based system to improve and potentially simplify the FDA BE regulatory standards. Clearly, a standard would have to be set on the product dissolution that would account for various excipient and formulation factors in a product.

Following the publication of the scientific paper in 1995 (10), the FDA continued internal discussion with additional scientists and public workshops. At this point, the FDA added a new scientist, Dr. Ajaz Hussain, to the BCS project, who continued to manage the FDA's internal development of the regulatory guidance. GLA returned to the FDA for several months in the spring of 1995 to work with Dr. Hussain and contributed to developing the BCS draft guidance. The BCS draft guidance was then reviewed internally at the FDA and in a series of expert meetings at the FDA. During this time period, 1995–1999, GLA, in addition to participating in the FDA conferences, made numerous public scientific presentations at public workshops, worldwide, sponsored by AAPS, FIP, and other organizations, fully testing out the scientific acceptance of the BCS approach. It was important that BCS have a sound, well-accepted scientific basis and support so that FDA would feel comfortable in moving away from an *in vivo* standard to an *in vitro* standard for ensuring BE. The BCS approach to BE regulation represented a major paradigm shift in BE regulatory standards for the FDA. The FDA had to be sure the BCS was sound and could withstand broad scientific evaluation and establish a solid scientific consensus.

The working draft of the BCS guidance was published in 1999 with a request for comments as is the norm. Surprisingly, only a few comments were made to the FDA on the draft guidance and the final guidance was published in August 2000, with essentially no changes (11). This was no doubt due to the extensive public presentations and discussions of the BCS approach prior to the release of the draft BCS guidance.

The well-accepted BE criteria, AUC and Cmax, are relatively empirical. They are not particularly mechanistic from the biopharmaceutic point of view. The drug dissolution standards, on the other hand, can be set on a mechanistic basis. If two drug products have the same *in vivo* dissolution profile under all luminal conditions, they will have the same rate and extent of absorption, and will be bioequivalent (10). The BCS places drugs in classes depending on the rate determining step controlling drug absorption. If the rate determining step is gastric emptying, which is the case for high-permeability drugs in solutions and in very rapidly dissolving immediate release (IR) dosage forms, then plasma levels do not provide any information relative to the biopharmaceutic differences in the two products tested (same API). This class of high solubility–high permeability–rapidly dissolving drugs is the first class in which the FDA allows *in vitro* standards to be used to ensure BE. For a high-permeability drug, which is well absorbed, it is not important to regulate on the basis of AUC since these drugs are completely absorbed (obviously a dissolution standard has to be met). Thus, the BCS approach simplified the BE regulatory requirements and initiated a scientific mechanistic basis for approaching BE.

BCS GUIDANCE

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability (11). When combined with the dissolution of the

drug product, BCS takes into account the three major factors that govern the rate and extent of absorption from immediate release solid oral dosage forms, namely, dissolution, solubility, and intestinal permeability (absorption). Using the principles of solubility and permeability, the drug substances can be classified into four classes: class 1—highly soluble and highly permeable; class 2—poorly soluble but highly permeable; class 3—highly soluble but poorly permeable; and class 4—poorly soluble and poorly permeable.

For regulatory use, boundaries had to be set on permeability, solubility, and dissolution. The starting point was the 8 oz (240 ml) of water taken with a typical *in vivo* BE study. This volume, plus the variable residual volume of liquid in the stomach of about 25–50 ml, lead to selecting a conservative volume of 250 ml for the solubility of the highest dose strength typically used in *in vivo* BE studies. Thus a *high-solubility drug* is based on the minimum thermodynamic equilibrium solubility over the pH range of 1–7.4. A suitable number of data points were suggested in the guidance including consideration of drugs with p*K*a's in the 3–5 range.

A *highly soluble drug* is defined as a drug where the highest marketed dose (highest dose strength) is soluble in 250 ml of aqueous media in over the entire gastrointestinal pH range (1.2–7.4), a conservative definition. A dosage form is usually marketed in several strengths and it was decided to use the highest strength that is marketed for the high-soluble drug determination. This is also the case with the BE studies, where the highest strength generally has to be used. Thus, a high-soluble drug is one that would be soluble over the entire pH range from the stomach through the upper small intestine.

"Highly permeable" means the extent of absorption (including intestinal and liver first pass metabolism) is greater than 90% of the dose administered. Absorption is, thus, taken to be the transport of the drug into the first cell, tissue, or interstitial fluid through the tight junctions between the intestinal epithelial cells. This definition was based on the human jejunal permeability database established based on permeability studies performed at the University of Uppsala and Michigan. The 90% fraction absorbed defines the lower limit for a highly permeable drug. Based on the FDA and Swedish MPA data base and additional intestinal permeability results, metoprolol (12–16) was selected as the reference drug. Recently, there have been several workshops and publications suggesting the relaxation of the absorption requirements from 90% to 85% and at the same time, to consider the aqueous media pH range to be 1.2–6.8 rather than 1.2–7.4. The initial permeability and dissolution limits were recognized as very conservative at the time of the draft guidance, but it was felt that more data and experience was needed to relax the standards. Permeability was determined in human intestinal jejunum. The permeability of metoprolol was designated as a cutoff point. Active pharmaceutical ingredients (APIs) having higher permeability were designated as highly permeable and APIs with lower permeability were classified as low permeable.

Dissolution test for the products is to be carried out under mild conditions, USP basket method at 100 rpm or paddle method at 50 rpm in pH 1.2, 4.5, and 6.8 aqueous buffer solutions, covering the stomach, duodenum and upper small intestine. The pH of 6.8 was chosen to be consistent with the current USP requirement. A pH of 6.5, the pH at which jejunal permeabilities (P_{eff}) were determined and representative of the average upper jejunal pH (6,8), was considered but the difference was considered small and of no consequence except potentially for very select drugs with p*K*a in the approximately pH ~6 range. The drug product should dissolve at least 85% in 15 min., or 30 min or less and should meet dissolution profile similarity criteria using *f*2 for the 30-min case, when compared with the reference product for biowaiver. According to the FDA Guidance, this was the first guidance having "waiver" in the title; only class 1 drug products are eligible for FDA biowaivers. For biowaivers, the dissolution of the test dosage form should be compared with the dissolution of the reference-listed drug (RLD) product.

The biowaiver guidance based on the biopharmaceutics classification system (BCS) suggests that documentation of bioequivalence *via* dissolution studies may be appropriate for BCS class 1 orally administered immediate release drug products. This waiver criterion is not applicable to narrow therapeutic index (NTI) drugs. This requirement was included based on safety considerations, though scientifically, it was less clear that it should be a requirement at the time of the draft guidance. A NTI drug product with a BCS class 1 drug that dissolved rapidly would again be rate limited by gastric emptying. However, the potential that excipients, tablet or capsule, or even shape, could alter gastric emptying could not be ruled out at the time of the draft BCS guidance and the conservative position of excluding NTI drugs for BCS-based biowaivers was included in the guidance.

Moving to an *in vitro* measure to ensure bioequivalence is a major paradigm shift, an extremely important step towards approval of drug products. Maintaining drug product safety, efficacy, and quality to the best of our scientific ability is essential. The dissolution testing for *in vivo* bioequivalence (dissolution profile comparison in multimedia representing the entire GI tract) is more elaborate than a typical single point quality control (QC) test. Thus BCS was established on sound scientific principles and has led to a major paradigm change in the bioequivalence (BE) standards for insuring drug product therapeutic equivalence.

WHO GUIDANCE

The Biowaiver Guidance issued by the FDA provided biowaivers for BCS class 1 drug products, *i.e.*, those which are highly soluble and highly permeable. This guidance has been viewed by several scientists to be highly conservative. A group of ten international scientists which included both of us (VPS and GLA), met under the auspices of WHO for 3 days to consider and discuss the extension of the BCS principles to provide biowaivers for other classes of drug products. It was concluded that drugs belonging to BCS class 3, *i.e.*, highly soluble but with low permeability and very rapidly dissolving can also be eligible for biowaivers (17). Taking these points into consideration, about 60%–70% of the drug products were identified in the WHO Essential Medicine List as being eligible for BCS-based biowaivers and can be approved for marketing based on dissolution criteria. This would reduce regulatory burden and make the drug products more affordable while insuring their quality. The WHO, while not

a regulatory body, has substantial influence on the setting of drug product regulatory standards in numerous countries around the world. It was felt that extending BCS would assist countries worldwide in insuring drug product therapeutic equivalence for a wider selection of essential medicines.

After the initial concept of BCS was proposed, it took almost 5 years before the BCS paper was published in 1995, and it took an additional 5 years before the final FDA guidance was published in August 2000, and an additional 6 years before the WHO guidelines using BCS for biowaivers was published. This additional length of time was primarily utilized in holding national and international conferences and workshops discussing BCS, and making sure that we were moving forward with a sound, widely accepted, science-based public policy on BE product standards. This illustrates that slow and necessary steps are needed to generate a scientific consensus and, most importantly, to incorporate scientific advance into public policy with its numerous additional issues.

BCS AND BDDCS

Analyzing a BCS classification of marketed drugs (18) in the four groups of the biopharmaceutics classification system, Wu and Benet made a very striking observation: drugs in classes 1 and 2 were highly metabolized whereas drugs in classes 3 and 4 were eliminated by liver or kidney as unchanged drug (19). In addition to this, Wu and Benet made many additional observations and predictions based on the BCS classification, and they termed this as "Biopharmaceutics Drug Disposition Classification System (BDDCS)."

While the BDDCS classification is based on a fraction metabolized and the BCS based on a fraction absorbed, the BCS and BDDCS are quite closely related. The two classifications are approximately 90% equivalent with the exceptions being, for example, drugs that are absorbed by an intestinal carrier-mediated transport mechanism, *i.e.*, polar and high permeability. BCS and BDDCS do have significant different purposes. The BCS is focused on oral intestinal absorption and is used to provide biowaivers for *in vivo* BE studies, based on solubility, permeability (absorption), and dissolution. On the other hand, the purpose of BDDCS is the prediction of the major route of drug elimination (drug disposition), transporter effect on drug absorption, transporters, and enzyme interplay and potential drug–drug interaction in the intestine and liver. The BCS and BDDCS together point to an exciting new era of molecular absorption, distribution, metabolism, and excretion (ADME).

LOOKING INTO THE FUTURE

As experience is gained by using BCS, and its usefulness is realized worldwide, further refinements of the regulatory requirements is very likely, particularly with regard to the most predictive *in vivo* dissolution methodology. This methodology will better reflect the *in vivo* dissolution conditions than the current QC dissolution requirement. This *in vivo* predictive dissolution methodology is a scientific area in need of significant future research studies to best define and set dissolution methodology standards. There is also a suggestion of further subdividing BCS class 2 and 4 drugs into weak acids, weak bases, and neutral compounds and to further develop dissolution requirements for biowaivers (20) based on this subclassification.

This subdivision, based on obvious physical chemical principles, may lead to the setting of dissolution methodologies based on drug class and sub class, and serve as a basis for further extension of the biowaiver approach to ensuring drug product therapeutic interchangeability.

The regulatory acceptance and even the harmonization process among all regulatory authorities will no doubt take considerable time. However, the process of establishing a scientific consensus is the essential starting point for public policy change. The BCS approach and the associated FDA guidance has set a new direction that will no doubt continue to be developed and provide a sound, mechanistic, scientific basis for setting pharmaceutical drug product performance standards that will be applicable worldwide.

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