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# Impact of Biopharmaceutics Classification System-Based Biowaivers†

**Jack A. Cook,‡ Barbara M. Davit,§ and James E. Polli*,||**

*Department of Clinical Pharmacology, Specialty Care Business Unit, Pfizer Inc., New London, Connecticut, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Rockville, Maryland, and Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, 20 Penn Street, Baltimore, Maryland 21201*

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**Abstract:** The Biopharmaceutics Classification System (BCS) is employed to waive *in vivo* bioequivalence testing (i.e. provide "biowaivers") for new and generic drugs that are BCS class I. Granting biowaivers under systems such as the BCS eliminates unnecessary drug exposures to healthy subjects and provides economic relief, while maintaining the high public health standard for therapeutic equivalence. International scientific consensus suggests class III drugs are also eligible for biowaivers. The objective of this study was to estimate the economic impact of class I BCS-based biowaivers, along with the economic impact of a potential expansion to BCS class III. Methods consider the distribution of drugs across the four BCS classes, numbers of *in vivo* bioequivalence studies performed from a five year period, and effects of highly variable drugs (HVDs). Results indicate that 26% of all drugs are class I non-HVDs, 7% are class I HVDs, 27% are class III non-HVDs, and 3% are class III HVDs. An estimated 66 to 76 million dollars can be saved each year in clinical study costs if all class I compounds were granted biowaivers. Between 21 and 24 million dollars of this savings is from HVDs. If BCS class III compounds were also granted waivers, an additional direct savings of 62 to 71 million dollars would be realized, with 9 to 10 million dollars coming from HVDs.

**Keywords:** Biopharmaceutics Classification System; biowaiver; bioequivalence; highly variable drugs; cost

## Introduction

Cook and Bockbrader previously examined the potential cost savings of using BCS-based waivers of *in vivo* bioequivalence studies (biowaivers) for class I drugs, in lieu of *in vivo* bioequivalence (BE) testing.[1] They considered the number of BE studies performed by the pharmaceutical industry between January 1998 and May 2001 and assumed 25% of BE studies are for class I drugs. They conservatively estimated in 2002 that "there is the potential to save one quarter the annual expenditures on BE studies, $22 to $38 million dollars/year". The authors only considered direct costs of testing and indicate that additional indirect savings can occur if BE studies are rate limiting to drug regulatory submission (e.g., avoid lost sales of over one million dollars per day if product leads to sales of $400 million per year) and if opportunity costs are considered (e.g., resources not deployed to running *in vivo* studies can be redeployed to bring other drugs to market faster). The analysis was limited to class I biowaivers.

* Author to whom correspondence should be addressed: Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, HSF2, room 623, Baltimore, MD 21201. Tel: 410-706-8292. Fax: 410-706-5017. E-mail: jpolli@rx.umaryland.edu.

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‡ Pfizer Inc.

§ U.S. Food and Drug Administration.

|| University of Maryland.

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Since 2002, several factors have changed that might lead to different cost savings estimates. First, several recent endeavors to classify large groups of drugs may lead to a more correct characterization of the proportion of drugs in each BCS class. Additionally, scientific consensus suggests biowaivers could be granted for immediate-release (IR) formulations of class III drugs that are very rapid dissolving, provided other concerns are addressed (e.g., stability, excipient effects, narrow therapeutic index).[2−4] More recently, both the World Health Organization and European Medicines Agency (EMEA) instituted guidance allowing BCS-based biowaivers for class III drugs.[5,6] Finally, it has been suggested that biowaivers can be granted for rapidly dissolving IR formulations of highly variable drugs that are not bio(equivalence) problem drugs.[7] The objective of this analysis is to estimate the economic impact of these potential expansions of the BCS. While the focus of analysis here is to estimate the economic impact, it should be noted that the main rationale for BCS-based biowaivers is that, in some situations, *in vitro* testing is at least as good as *in vivo* testing in determining BE of IR solid oral dosage forms, and sometimes better in terms of direct assessment of product performance and avoiding unnecessary human exposures.[7]

## Frequency of Class I and Class III Drugs

Several authors have attempted to classify large groups of drugs.[8−10] Table 1 lists the relative distribution of drugs across the four BCS classes. Approximately two-thirds of these drugs are highly soluble, with approximately one-third classified as class I and one-third class III. These distributions agree with that of Benet and Wu, who, in proposing a Biopharmaceutics Drug Disposition Classification System (BDDCS), extensively examined 169 drugs in the WHO Essential Medicines List.[11] These 169 compounds showed 39%, 30%, 26%, and 8% for BDDCS class I, II, III, and IV, respectively. These distributions are further supported by Khandelwal et al., where drug disposition data for 56 previously unclassified drugs was obtained from an extensive literature search.[12] These 56 compounds were distributed within BDDCS class I, II, III, and IV as 47%, 20%, 25%, and 9%, respectively. It should be noted that analysis here reflects compounds that have already been developed and approved; future drug distribution may differ (e.g., more low solubility drugs).

***Table 1.*** Distribution of Drugs in the BCS Classes[a]

| grouping[b] | class I | class II | class III | class IV | ref |
|---|---|---|---|---|---|
| top 200[c] | | | | | 8 |
| United States | 34 | 33 | 25 | 7 | |
| Great Britain | 33 | 32 | 28 | 7 | |
| Spain | 32 | 33 | 31 | 5 | |
| Japan | 36 | 35 | 24 | 4 | |
| WHO Essential Medicines | 36 | 17 | 38 | 9 | 9 |
| WHO Essential Medicines | 29 | 20 | 38 | 13 | 10 |
| highly variable drugs | 24 | 21 | 10 | 45 | derived here from ref 15 |

[a] Values are percentages, based only on those drugs that have been classified. [b] Values are for oral immediate release products. [c] Values are obtained from graph and are rounded so total may differ from 100%.

## Frequency of Highly Variable Drugs (HVDs) for Possible Additional Biowaiver

HVDs are drugs characterized by within-subject variability (% CV) in Cmax or AUC of 30% or more.[13] In general, in order to gain marketing approval, these HVDs typically are approved for administration at regimens in the flat portion


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of the dose response curves (i.e., near maximal effect) in order to ensure that adequate exposure is consistently achieved across the target patient population. As a consequence, HVDs exhibit large therapeutic windows, such that clinically important adverse drug reactions (ADRs) occur at much higher doses than those required for efficacy.[14] Davit et al. reviewed over 1000 *in vivo* BE studies of 180 different drugs, of which 31% were highly variable.[15] About 60% of the HVDs were highly variable due to drug substance pharmacokinetic characteristics. Formulation performance contributed to the high variability only about 20% of the time; thus high variability is frequently not due to poor product quality.[15]

From this report,[15] the BCS classification distribution of the 29 drugs that were consistently highly variable was 24%, 21%, 10%, and 45% for BCS class I, II, III, and IV, respectively (Table 1).[15] Hence, an estimated 66% of HVDs are either class II or class IV drugs, with 34% being class I or class III drugs. The BCS class distribution of HVDs is notably enriched in class IV drugs and contains notably fewer class III drugs. Contributions of lipophilicity/metabolism to higher drug variability would anticipate these differences. Assuming 31% of drugs are HVDs and that HVDs are distributed across classes I and III as 24% and 10%, respectively, 26% of drugs are non-HVDs in class I, 7% drugs are HVDs in class I, 27% of drugs are non-HVDs in class III, and 3% drugs are HVDs in class III (Table 1). Of course, these values are estimates.

It is well-appreciated that *in vivo* BE studies of HVDs often require using a greater number of subjects than non-HVDs, in order to avoid type II error. Tanguay et al. examined over 1200 BE studies performed between 1992 and 2002 and observed the failure rate increased as intrasubject variability increased, reaching an astounding 85% when intrasubject CV was greater than 35%.[16] The authors suggested that this likely occurred in an attempt to control study power and cost, and address ethical issues and logistical difficulties, simultaneously.

As discussed below, estimating the potential direct cost savings by employing BCS-based biowaivers for HVDs is complicated by a number of factors. More subjects are needed for the *in vivo* BE testing of HVDs compared to the number of subjects needed for non-HVD trials. However, it appears that insufficient numbers of subjects are being used in HVD BE trials as the study failure rate increases with intrasubject variability (which is associated with sample size). For example, the failure rate of studies using $n = 49$ to 60 subjects was three times larger than the failure rate of studies using $n = 37$ to 48 subjects.[16] Because of the high subject numbers per study and the higher failure rate of studies with HVDs, the potential direct cost savings for HVDs could be much larger than that for non-HVDs, which suffer less from this encumbrance. It is recognized that the distribution of HVDs in the BCS is somewhat different from for non-HVDs. Most notably, there are fewer highly soluble compounds (class I and III) among HVDs compared to all drugs (Table 1). Yet, one-third of HVDs are highly soluble and, at least for these drugs, one would expect formulation differences to have minimal impact on bioavailability as the drugs should go quickly into solution. For these drugs, it would seem that *in vitro* dissolution based testing would be the best way to establish BE.

## Economic Impact of Biowaivers of Class I Drugs and Class III Drugs

To estimate the potential economic impact of biowaivers for BCS class I and III compounds, the number of BE studies conducted each year was calculated. To avoid counting the same studies more than once, only data submitted to the US FDA were considered. It was recognized that this approach would likely underestimate the actual numbers of studies performed. Between January 1, 2004, and December 31, 2008, there were 1119 Abbreviated New Drug Applications (ANDAs) approved for solid oral formulations.[17] The current FDA guidance on establishing BE under fed conditions generally recommends both fed and fasted BE trials for all solid oral dosage form ANDAs, with few exceptions.[18] Thus, each submission was assumed to contain two trials. These data indicate that, on average, 448 *in vivo* BE trials are conducted per year in support of ANDAs. This value is likely an underestimate in that it assumes no failed trials and does not account for formulations that were once under development but never submitted.

For New Drug Applications (NDAs), a calculation is more complex due to the high attrition rate of new molecular entity compounds.[19] Between January 1, 2004 and December 31, 2008, there were 43 NDAs approved for solid oral formula-

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tions of new molecular entities.[17] To determine the number of *in vivo* BE trials per year for these products, the number of compounds in development leading to 8.6 approvals/year was determined as follows. The attrition rates determined by Kola and Landis were assumed to be applicable.[19] The average time between the initiation of human studies and approval is assumed to be approximately 8 years.[20] It was also assumed that no BE trials are conducted during the initial year of human studies or in the last year, when the drug is undergoing regulatory review; this essentially means that BE trials are only conducted during phase II and III development. Under these assumptions, 19.4 compounds would be in phase II and III for each approval. A typical NDA submission contains 3 to 6 BE trials,[1] so these trials are conducted at a rate of 0.5 to 1 per year. Thus, to support the 8.6 approvals/year for new molecular entities, 84 to 167 BE studies are conducted per year (8.6 × 19.4 × 0.5 to 1). In addition, between January 1, 2004, and December 31, 2008, there were 11.8 approvals/year for new salt forms, manufacturers or new formulations.[17] Assuming that, similar to ANDAs, at least two *in vivo* BE studies are performed to support their approvals, this represents an additional 24 studies/year. All totaled, it is estimated that 555 to 639 *in vivo* BE studies are performed each year.

Costs associated with 2-way crossover bioequivalence trials were estimated for studies involving different numbers of subjects. A value of 32 subjects was used for a typical study.[15] The following sample sizes were used for various HVD scenarios. Sixty-four subjects were used to characterize a typical HVD study, since a typical HVD has an intasubject RSME (log scale) of 0.325 and 64 subjects are needed for at least a 90% probability of declaring BE with a true difference of no more than 5%. For an extreme HVD scenario, we estimated that, on average, 146 subjects are needed to demonstrate BE between two products, as the 90th percentile of HVDs have an intrasubject RSME (log scale) of 0.5 and 146 subjects are needed for at least 90% probability of declaring BE with a true difference of no more than 5%.[15] The estimated costs for these trials are approximately $320,000, $510,000 and $1,000,000, respectively. These costs include expenses associated with clinic use, drug assay, data management, programming, writing, and monitoring.

Assuming that 31% of all drugs are highly variable[15] and that one-quarter of the HVDs and one-third of all others are BCS class I (Table 1), one would expect to save between 66 and 76 million dollars each year in clinical study costs if all class I compounds were granted biowaivers. Between 21 and 24 million dollars of these savings come from granting biowaivers for HVDs. If BCS class III compounds were also granted biowaivers, as is now allowed in EMEA guidelines,[6] there is projected an additional savings of 62 to 71 million dollars, with 9 to 10 million dollars coming from biowaivers of studies of HVDs.

There are further reasons to consider these as underestimates of the true value of biowaivers. In the USA, if the to-be-marketed formulation differs from the pivotal clinical trial formulation, BE must be assessed to link the two formulations.[21] If BE trials are rate-limiting to filing (and hence to approval), dissolution testing can be more rapid than BE testing. It is estimated that there is a savings of at least 6 weeks in development time between performing dissolution tests needed for a BCS based waiver and the time to perform an *in vivo* trial. Considering a drug with sales of one billion dollars per year, this savings would generate an additional 110 million dollars in sales. Direct development costs are another consideration. The 85% failure rate for drugs with CVs greater than 35% likely means that HVDs undergo more BE testing than done for typical drugs. This suggests that applying more biowaivers for HVDs will lead to substantial savings, given the larger size of the trials and the high numbers of trials being performed, both of which prolong drug development.[22] The fact that approximately 34% of these HVD compounds are highly soluble (Table 1) suggests that there is a significant proportion of these compounds for which BE should not be problematic and their failure rate is unnecessarily high.

Of course, drug development based on BCS-based biowaivers nonetheless incurs costs, including solubility, permeability, and dissolution studies. Assuming that 33% and 30% of the annual 555 to 639 BE studies concern class I and III drugs, respectively, and that a BCS-based study incurs a cost of $50,000 to $100,000, about 2 to 4 million dollars is needed each year to carry out BCS-based biowaivers (about equally distributed between class I and III compounds). These costs are considerably smaller than the annual savings through reduced *in vivo* BE testing, which are between 66 and 76 million dollars for class I compounds and 62 to 71 million dollars for class III compounds.

We admit that the scale of these direct cost savings are modest, relative to the costs incurred across the entire pharmaceutical industry, particularly since demonstration of BE is but one aspect of the many activities within the pharmaceutical industry. Nonetheless, we believe that opportunities to reduce regulatory burden and costs of conducting *in vivo* studies, and as well as the importance of decreasing unnecessary human testing,[21] support the need for the pharmaceutical industry to become even more efficient.[19,23]

Additionally, substantial indirect savings can occur if BE studies are rate limiting to drug development. It is not unusual for BE trials to be rate limiting for regulatory filing. Such BE trials typically involve commercial formulation evaluation

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or manufacturing site transfer. In these cases, it is not unreasonable to assume that *in vitro* BE results can be obtained six weeks earlier than *in vivo* BE trial results. This time savings translates into a potential additional 110 million dollars in sales from a six week earlier approval of a drug with eventual sales of 1 billion dollars a year. Further, by not running a human BE trial, clinical resources are freed to be applied elsewhere.

## Other Considerations

While the focus of analysis here is to estimate economic impact, it should be noted that the main rationale for BCS-based biowaivers is that, in some situations, *in vitro* testing is at least as good as *in vivo* testing in determining BE of IR solid oral dosage forms, and sometimes better.[7] In addition to reducing costs, *in vitro* studies can actually be better than *in vivo* studies in some instances because *in vitro* studies more directly assess product performance and offer benefits in terms of ethical considerations. *In vitro* studies more directly assess product performance than do conventional human pharmacokinetic BE studies, since *in vitro* studies focus on comparative drug absorption from the two products, while *in vivo* BE testing can suffer from complications due to its indirect approach. This indirect nature of *in vivo* pharmacokinetic testing is especially evident from HVDs. We suggest that it makes little sense, in evaluating BE of an IR solid oral dosage forms of a class I or III drug, to prefer a human pharmacokinetic study over an *in vitro*-based approach, especially for HVDs that are class I or III and suitably formulated (e.g., rapidly dissolving if class I and very rapidly dissolving if class III). Regarding ethical considerations, *in vitro* studies better embrace the principle "No unnecessary human testing should be performed"[21] and can result in faster development.

In practice, a complete realization of benefits of BCS-based biowaivers is not achievable as long as inter-regulatory differences exist. For example, while the USA,[24] EMEA,[6] and WHO[25] allow dissolution-based biowaivers based on BCS classification, Japan does not.[26] Thus, in the absence of harmonization among worldwide regulatory agencies with respect to criteria necessary to obtain a BCS-based biowaiver, global pharmaceutical companies will choose to demonstrate BE by a methodology that will allow acceptance by any country. This suggests that drug developers will continue to default to human testing, although such testing is not necessarily better, involves a higher cost, and puts participating healthy volunteers at (minimal) risk. There is also historical reluctance within pharmaceutical companies to pursue BCS-based biowaivers due to a perceived uncertainty of regulatory success. For example between 2000 and 2009, of 83 approved ANDAs for 16 different BCS class I drugs, 64 of these approvals were based on acceptable *in vivo* BE studies, with only 19 were based on acceptable BCS class I biowaiver requests. These data suggest that regulatory uncertainty still exists regarding the feasibility of submitting regulatory applications requesting BCS-based biowaviers in lieu of *in vivo* BE studies. Thus, to allay concerns about regulatory uncertainty, sponsors only need to ensure that they are submitting petitions in accordance with the FDA guidance.

It should be noted that the historical reluctance within pharmaceutical companies to pursue BCS-based biowaivers appears to be diminishing. Although it has been 11 years since implementation of the BCS guidance, BCS-based biowaiver requests have accelerated in only the last couple of years. Since FDA first posted its BCS guidance in 2000, it has designated 27 drugs as class I. Of these, BCS class I designation arose from biowaiver requests in 14 NDAs, 10 ANDAs, and 3 Investigational New Drug Applications (INDs). We are unaware of any case where a product was approved on the basis of a BCS-based biowaiver and then subsequently found to exhibit bioinequivalence *in vivo* (i.e., that prediction from favorable BCS properties was incorrect).

In summary, the BCS is employed to provide biowaivers for new and generic drugs that are BCS class I. Granting biowaivers under systems such as the BCS eliminates unnecessary drug exposures to healthy subjects, reduces regulatory burden, and provides economic relief, while maintaining the high public health standard for therapeutic equivalence. International scientific consensus suggests class III drugs are also eligible for biowaivers. The objective of this study was to estimate the economic impact of class I BCS-based biowaivers, along with the economic impact of a potential expansion to BCS class III. Methods consider the distribution of drugs across the four BCS classes, numbers of *in vivo* bioequivalence studies performed from a five year period, and effects of

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HVDs. Results indicate that 26% of all drugs are class I non-HVDs, 7% are class I HVDs, 27% are class III non-HVDs, and 3% are class III HVDs. An estimated 66 to 76 million dollars may be saved each year in clinical study costs if all class I compounds were granted biowaivers. Between 21 and 24 million dollars of this savings is from HVDs. If BCS class III compounds were also granted waivers, an additional direct savings of 62 to 71 million dollars may be realized, with 9 to 10 million dollars coming from HVDs.

## Abbreviations Used

BCS, Biopharmaceutics Classification System; HVDs, highly variable drugs.

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