GLOBAL ACCEPTANCE

one test

BIOWAIVER APPROVED

What you need to know about BCS Biowaivers

FUNDAMENTAL QUESTIONS
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The Biopharmaceutics Classification System (BCS) remains underutilized in drug development. It is a regulatory pathway through which, in some cases, a drug developer can avoid clinical bioequivalence studies based solely on \textit{in vitro} solubility, permeability, and dissolution data. It can save significant time and money in drug development, and is endorsed by the World Health Organization as a way of making generic drugs more readily available to the global population. The most obvious application is for generics, and it is used frequently in that context, but it also applies to new drugs.

Absorption Systems performs more \textit{in vitro} BCS studies than any other CRO in the world; probably more than any other company, pharma included. So we think about this all the time and are acutely aware of numerous subtleties that allow for a greater utilization of this scientific framework.
WHAT IS BCS?

The Biopharmaceutics Classification System (BCS) classifies drugs according to their aqueous solubility and intestinal permeability. Since drug dissolution, solubility, and gastrointestinal permeability are the three major factors governing the rate and extent of oral absorption, the parameters of this classification scheme provide a basis for in vitro-in vivo correlations and estimating the absorption of drugs. See Amidon’s seminal paper for additional background (Amidon et al., 1995).

BCS divides compounds into four categories

• Class I - High Solubility, High Permeability
• Class II - Low Solubility, High Permeability
• Class III - High Solubility, Low Permeability
• Class IV - Low Solubility, Low Permeability

BCS Class I compounds (high solubility, high permeability), in rapidly dissolving, immediate-release (IR) solid oral dosage forms, are eligible for waivers of clinical bioequivalence (BE) and certain drug-drug interaction (DDI) studies.
**WHAT IS A BCS BIOWAIVER?**

BCS is a regulatory mechanism through which drug developers and generic companies can obtain a waiver of clinical BE studies, also called a biowaiver. According to the USFDA BCS Guidance, highly soluble and highly permeable compounds (i.e. BCS Class I) in an immediate-release (IR) solid oral dosage form are eligible for biowaivers. For such compounds, the rate and extent of drug absorption is unlikely to be affected by drug dissolution and/or gastrointestinal residence time, and *in vivo* BE studies (for new formulations, line extension, post-approval changes, etc.) may be waived based on *in vitro* permeability and solubility data.

The FDA formally acknowledged that this classification supports *in vivo* bioavailability and bioequivalence waivers in its 2000 Guidance (Guidance for Industry: Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System), which states “when the *in vivo* dissolution of an IR solid oral dosage form is rapid in relation to gastric emptying and the drug has high permeability, the rate and extent of drug absorption is unlikely to be dependent on drug dissolution and/or gastrointestinal transit time. Under such circumstances, demonstration of *in vivo* BA or BE may not be necessary for drug products containing class I drug substances … ”

Furthermore, for Class I compounds, it is unlikely that intestinal absorption will be limited by efflux transporters. Thus, it may be possible to waive some clinical DDI studies as well: in the 2012 Guidance for Drug Interaction Studies, the USFDA states that clinical DDI studies for substrates of intestinal efflux transporters could be waived for BCS I compounds.
**WHY IS BCS IMPORTANT?**

Knowing the BCS class of a compound enables you to predict its *in vivo* absorption, disposition (transporter and metabolism interactions), potential for food effects, guide your formulation strategy (and the impact of scale-up and post approval changes), and potentially waive clinical studies. The Biopharmaceutics Drug Disposition Classification System (BDDCS) extends the concept of BCS to predict the extent of metabolism, and was derived from the observation that most BCS I and II (high permeability) compounds are substantially eliminated by metabolism, whereas BCS III and IV (low permeability) compounds are eliminated largely unchanged into the bile and/or urine (Wu et al., 2005).
WHAT ARE THE BENEFITS OF A BCS BIOWAIVER?

There are tremendous benefits in time and cost when in vitro experiments can be used as a surrogate for clinical studies, not to mention the ethical benefit of eliminating unnecessary human testing.

In vitro data is inherently less variable than clinical pharmacokinetic data. This is particularly true for compounds that are extensively metabolized, for which, in addition to the plasma area under the concentration-time curve (AUC) of the parent compound, urinary recovery of parent compound and urinary and fecal recovery of Phase I and Phase II drug metabolites must be monitored in order to determine the fraction absorbed.

Each molecule has its own unique challenges and a BE study may not always be the best option, especially for drugs belonging to one of the following categories:

- a drug with severe side effects (nausea, sedation, etc.)
- a drug that needs to be administered to patients rather than healthy volunteers (e.g., cytotoxic anticancer drugs)
- a drug with addictive or abuse potential
- highly variable drugs

BCS biowaivers are independent of therapeutic class and pharmacokinetics:

Approximately 30% of all oral, immediate-release drugs can be classified as highly permeable and highly soluble, and it has been estimated that the pharmaceutical industry could realize over $128 million per year in direct savings through implementation of the BCS (Cook et al., 2010).

From a financial perspective, the avoidance of a BE study can help save a generic company several hundred thousand dollars in development costs. In addition, use of the BCS approach can eliminate the need for unnecessary human testing.

From a timeline perspective, the benefit to using the BCS approach is that the required solubility and permeability studies can be performed in parallel with formulation development. Additionally, if these studies are executed early in the development process, the overall development timeline can be reduced by several months.
Fed/Fasted

II. In vivo option: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in-vivo
   Strength: 15 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments:

2. Type of study: Fed
   Design: Single-dose, two-way crossover in-vivo
   Strength: 15 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments:

Parent and Metabolite

Analytes to measure (in appropriate biological fluid):
and its active metabolite monohydroxylated
in plasma.

Special Population

Type of study: Fasting
Design: Single-dose, two-way crossover in vivo with dosing on the first 2 days of a treatment cycle
(i.e., Period 1 and Period II of the study are Day 1 and Day 2, respectively, of the treatment cycle)
Strength: 250 mg (dose 1x250 mg)
Subjects: Cancer patients who are already receiving or are about to start receiving 250
mg once daily as their calculated individualized dose (e.g. based upon factors such as tumor type,
body surface area, cycle number and toxicity). All subjects who received at least one dose of the
investigational drug (i.e., the safety population) should be included in the assessments of safety and
tolerability.
Additional Comments: Submission of an Investigational New Drug Application (IND) is required
prior to conducting a bioequivalence study for a cytotoxic drug product such as [blank] (see 21
C.F.R § 320.31).

Special Population with Reference Scaled Approach

Type of study: Fed
Design: Single-dose, two-way, crossover in-vivo
Strength: 500 mg
Subjects: Cancer patients already receiving a stable twice-daily dosing
regimen as prescribed by the reference product label (i.e. 1250 mg/m², twice
daily, equivalent to 2500 mg/m² total daily dose, for two-weeks followed by a
one-week rest period given as three-week cycles)
Additional Comments: See comments below:
HOW IS A BIOWAIVER POSSIBLE?

The primary determinants of oral absorption are (in the order in which they occur) 1) dissolution, 2) solubility, and 3) permeability. For an immediate-release solid oral dosage form that is BCS I (high solubility, high permeability) and exhibits rapid dissolution, none of these determinants are limiting, and therefore oral absorption will be complete (90% or more), assuming the compound is stable in the gastrointestinal tract and the formulation consists of excipients that do not significantly affect absorption of the active ingredient.
What Is the Price for a BCS Biowaiver?

The price of an *in vitro* classification study may vary depending on the specific characteristics of the compound, but will undoubtedly be lower than a corresponding clinical study.

The *in vitro* approach is especially favorable to obtain a direct measurement for compounds that exhibit high variability or present other challenges in the clinic, such as:

- a drug with severe side effects (nausea, sedation, etc.)
- a drug that needs to be administered to patients rather than healthy volunteers (e.g., cytotoxic anticancer drugs)
- a drug with addictive or abuse potential
- highly variable drugs

Besides the lower direct cost of an *in vitro* study vs. a clinical BE study, the savings in development time realized from bypassing clinical studies during new drug development is projected to translate into $50-$150 million in additional potential revenue per drug product. Resources and time may then be spent on other projects, enabling higher throughput of drug products (Cook et al., 2010).

Class I and Class III compounds make up 61% of drugs that have been classified. Projected annual savings if biowaivers were used for all Class I and Class III compounds is between $128 and 150 million (Cook et al., 2010).
HOW MUCH TIME DOES A BIOWAIVER TAKE?
At Absorption Systems, biowaiver eligibility may be determined in 1 to 2 weeks using non-GMP material. Since we use conservative conditions for this assessment, a positive result is always indicative of high permeability. So, essentially, in 1 to 2 weeks you will know if your compound has BCS I permeability and you can adjust your development strategy accordingly.

The entire study (eligibility screen through pivotal phase) takes approximately 6 weeks to complete. Upon submission to the USFDA, the ANDA review and approval process with data from a BCS biowaiver is no different than with data from and in vivo BE study.

WHAT ARE THE CHANCES THAT THE FDA WILL ACCEPT THE WAIVER REQUEST?
While the FDA may ask questions or require clarification regarding study results, in the 10+ years that Absorption Systems has been performing these studies, there has not been an instance of the biowaiver being rejected for a compound that meets the BCS eligibility criteria for a biowaiver.
WHAT ARE THE DRAWBACKS OF OPTING FOR AN *IN VITRO* BIOWAIVER INSTEAD OF A CLINICAL BE?

*In vitro* studies reduce timelines and development costs, and eliminate unnecessary human testing. The *in vitro* test system employed by Absorption Systems (based on the Caco-2 cell monolayer model) is an intrinsically conservative test system, which has never over-estimated the absorption of a compound (i.e., no false positives). The only “drawback” is that BCS biowaivers are only appropriate for certain types of products—i.e., BCS I (or III) immediate release solid oral dosage forms.

HOW MANY BIOWAIVERS HAVE BEEN GRANTED?

Absorption Systems has classified over 100 unique compounds using a validated test system. Many of these classifications are included in submissions already approved or currently under review for both new and generic drugs. To our knowledge, none have been rejected for regulatory approval.
References


Why Absorption Systems?

Absorption Systems is the world leader in applying the Biopharmaceutics Classification System for BCS based biowaivers. Our experience, which spans more than a decade, translates into innovative solutions, such as a novel high permeability standard, which enables the most accurate classification available, and a pre-qualification step that allows for early identification of BCS biowaiver candidates.

Our extensive experience continues to facilitate innovative solutions and enable *in vitro* classification for a broad range of drugs across all therapeutic classes. This, combined with our 10-day turnaround for pre-qualification and our cost effective designs, saves you time and money. Just a few reasons why Absorption Systems averages more than 30 BCS studies each year.

Eight of the ten largest generic drug companies and dozens of other small and large pharmaceutical companies have conducted *in vitro* BCS biowaiver studies with Absorption Systems.

Learn more about BCS at absorption.com/bcs
About Absorption Systems
Absorption Systems assists pharmaceutical and medical device companies in identifying and overcoming ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) barriers in the development of drugs and medical devices. The company’s mission is to continually develop innovative research tools that can be used to accurately predict human outcomes or to explain unanticipated human outcomes when they occur. The CellPort Technologies® platform, a suite of human cell-based test systems for drug transporter characterization, exemplifies Absorption Systems’ commitment to innovation. The company’s facilities are strategically located on both US coasts and Panama, and encompass nearly 65,000 sq. ft., servicing hundreds of customers throughout the world. For more information on the company’s comprehensive contract services and applied research programs, please visit absorption.com.

Preclinical Services & Capabilities

Lead Optimization
Physicochemical Properties
Permeability
Stability
Metabolism and Transporters
Binding and Distribution
Formulation Assessment
Bioavailability and Exposure | rodent, non-rodent

Candidate Selection
Formulation Development
PK and Biodistribution | multiple species and dose routes
Barriers to Bioavailability
In Situ and Isolated Organ Perfusion | rat: brain, liver, intestine
Ex Vivo Tissue Permeability | intestinal, dermal, ocular, buccal, nasal, vaginal

IND- and NDA-Enabling
Transporter-Based Drug Interactions
BCS Permeability and Solubility
Classification for Biowaivers
Metabolism-Based Drug Interactions
Metabolite ID and Production
Medical Device Testing
Toxicology

Bioanalysis
Bioanalytical Support from Discovery through Clinical
GLP and Non-GLP

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