GLOBAL ACCEPTANCE

What you need to know about BCS Biowaivers

REGULATORY REQUIREMENTS AND APPROVAL PROCESS
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Introduction

For over 13 years, the USFDA has advocated the Biopharmaceutics Classification System (BCS) as a regulatory mechanism for drug developers and generic companies to obtain waivers of clinical bioequivalence studies, also known as biowaivers. Acceptance and application of this system has proliferated, as other international regulatory agencies have followed this precedent.

The in vitro approach to the BCS, is a reliable, inherently conservative, scientifically proven approach and, when performed correctly using a validated test system:

1) It eliminates unnecessary human testing
2) It shortens development time and therefore overall product costs
3) It is the most definitive approach to establish equivalence

Biowaivers have been applied to a broad range of drugs across a multitude of therapeutic classes, including those which require special patient populations for clinical BE, and drug substances that are highly variable due to their pharmacokinetics.

This is possible as the BCS based biowaiver is a framework that has been developed around three simple measurements: two on the active pharmaceutical ingredient (API) – solubility and permeability – and a third on the finished dosage form – dissolution. Results from these three evaluations provide direct assessment of dosage form performance and, when certain conditions are met, make bioequivalence self-evident. When the API and the finished dosage form meet these established criteria, then we know unequivocally that the test product will be therapeutically equivalent to the marketed (“approved” or “reference”) product.
Eligibility

WHEN CAN YOU APPLY FOR A BIOWAIVER?
Both new and generic drugs are eligible for BCS biowaivers. Subsequent in vivo bioavailability (BA) or bioequivalence (BE) studies after establishment of initial bioavailability may be waived. Certain drug-drug interaction studies may also be waived for new drugs. Biowaiver applications may be included in the following submissions:

- IND: for new drugs under development
- NDA: to market new drugs
- ANDA: to market generic drugs

Between 2003 and 2011, dozens of drug products were submitted to FDA for BCS biowaivers – 46% for generic drugs and 54% for new drugs (Nair et al., 2012; Davit et al., 2011).

WHEN ARE BCS BIOWAIVERS NOT APPLICABLE?
Exceptions include narrow therapeutic index (NTI) drugs and dosage forms intended for absorption in the oral cavity (e.g., sublingual or buccal tablets). Otherwise, any BCS I compound in a rapidly dissolving, immediate-release, solid oral dosage form is eligible for a biowaiver.

NTI Drugs
- Subject to therapeutic drug monitoring
- Product labeling indicates a narrow therapeutic range designation
- Examples: theophylline, warfarin, digoxin

Products designed to be absorbed in the oral cavity
- Sublingual tablets
- Buccal tablets
CAN BCS BIOWAIVERS APPLY TO PRODRUGS?
It depends on the mechanism and anatomical site of conversion from the prodrug to active. If conversion occurs after intestinal absorption, then it may be sufficient to determine the permeability of the prodrug only. If conversion occurs prior to absorption, then it may be necessary to determine the permeability of both the pro-drug and the active drug.

ARE BIOWAIVERS APPLICABLE FOR DRUGS OTHER THAN BCS CLASS I?
The US FDA currently accepts biowaivers only for BCS I, although Class III is under consideration. While scientific justification may be considered for BCS II and III compounds in certain cases, these are not formally recognized under the current US BCS guidelines. According to the EMA and the draft Health Canada guidelines, BCS biowaivers apply for both BCS I and III compounds.

WHICH THERAPEUTIC CLASSES ARE ELIGIBLE FOR BCS BIOWAIVERS?
BCS biowaivers are independent of therapeutic class or pharmacokinetics of the drug substance.

Generic Drugs by Therapeutic Class: Absorption Systems Biwaiver Experience

- ADHD – 7%
- Alzheimer's/Parkinson's – 12%
- Analgesic – 10%
- Smoking Cessation – 2%
- Epilepsy/Seizures – 5%
- Insomnia –5%
- Anxiety/Depression – 10%
- Schizophrenia – 2%
- Muscle Relaxant – 2%
- 2% – Urinary Incontinence
- 2% – Sjogren's Disease
- 2% – Glaucoma
- 5% – Antiemetic
- 2% – Gaucher's Disease
- 2% – Antimalarial
- 17% – Anticancer
- 2% – Antibiotic
- 7% – Antihistamine
HOW IS THE BCS WAIVER OPTION ADDRESSED IN USFDA GENERIC DRUG GUIDANCES?

The USFDA posts bioequivalence recommendations for generic drug products on their website. The guidance is called “Bioequivalence Recommendations for Specific Products” and includes listings for hundreds of drugs. It is our understanding that if absorption data for a Class I drug are publicly available or if a generic manufacturer has chosen the BCS biowaiver path to establish therapeutic equivalence, then the USFDA may update the corresponding individual product BE guidance to read, “Recommended studies—2 Options: BCS Waiver or In-vivo Studies.”

WHAT DOES IT MEAN IF THE IPR MENTIONS THE BCS WAIVER OPTION? DO I STILL NEED TO COMMISSION A STUDY TO DETERMINE BIOWAIVER ELIGIBILITY?

If the IPR denotes BCS waiver option, it means that a firm can explore a BCS waiver if the firm believes that a drug substance and drug product meet BCS class I criteria. It does not mean that the FDA has classified this as BCS I or that the IPR can be used as the basis for requesting a waiver of BE studies.

It is necessary for the sponsor to submit classification data (from a validated test system with a qualified high permeability standard) to support a biowaiver application. A complete application includes appropriate documentation including high solubility, high permeability and rapid dissolution as detailed in the Guidance for Industry.

Even if the IPR does not state BCS waiver option, a firm may request a BCS biowaiver if the compound and product meet the requisite criteria.
IS THERE A LIST OF PRODUCTS ELIGIBLE FOR BCS BIOWAIVERS?

The USFDA explicitly recommends the ‘BCS waiver option’ for at least 25 molecules. This option is listed in the corresponding IPR, which may be found on the USFDA website.

The European agency, EMA, is in the process of preparing product-specific recommendations for BE, and compounds eligible for BCS biowaivers will likely be noted. The Brazilian agency, ANVISA, has published a list of compounds for which biowaivers are acceptable.

BCS classification data may be found in published literature. For example, the WHO published classification data for an essential medicine list (EML). It is important to note, however, that even for these compounds it is necessary for the sponsor to submit classification data (from a validated test system with a qualified high permeability standard) to support a biowaiver application.

In other words, published literature or an IPR alone is insufficient to receive a BCS biowaiver from USFDA. This was echoed in a recent regulatory note which states, “…FDA considers granting biowaivers only for Class I drugs but does not use the WHO BCS list to grant such biowaivers. Rather the USFDA follows the criteria described in its Guidance for Industry on the BCS and considers the applicant’s submitted solubility/permeability data on API and dissolution data on the drug product in deciding whether a Class I biowaiver is appropriate” (Nair et al., 2012).

Most importantly, it must be noted that any compound that meets the requisite dissolution, solubility, and permeability criteria is eligible for a BCS biowaiver regardless of whether the “BCS Waiver” option is stated in the individual product recommendation.
Regulatory Approval Process

HOW ARE BCS BIOWAIVERS APPLIED FOR CLASS I NEW DRUGS?
Once the USFDA informs the firm of their decision, subsequent in vivo BE studies during development are waived, including:

• Formulation development, e.g., clinical trial formulation versus to-be marketed formulation
• Line extensions, e.g., new strengths or new formulations for a different population
• Certain types of post-approval changes, e.g., manufacturing site change or manufacturing process

HOW LONG DOES IT TAKE TO RUN A BCS CLASSIFICATION STUDY? HOW LONG FOR BIOWAIVER APPROVAL OF AN ANDA?
The entire study (eligibility screen through pivotal phase) takes approximately 6 weeks to complete. The review and approval process is no different than an ANDA filed with in vivo BE data.

WHAT ARE REASONS THAT A BIOWAIVER SUBMISSION WOULD BE REJECTED?
If a submission is complete and the active ingredient and drug product meet the requisite criteria, then the biowaiver submission should never be rejected. Reasons that a submission may be rejected include (Nair et al., 2012):

• Lack of multi-pH solubility profile
• Inappropriate method of solubility determination
• Lack of dissolution data for all strengths
• Missing SOPs for analytical methods
• Missing data supporting gastrointestinal stability
• Lack of data on efflux transporters in the cell line used for in vitro permeability
• Lack of bidirectional in vitro permeability data on control model compounds

DO WE NEED TO FILE ANY DOCUMENTS OR OBTAIN PRE-APPROVAL FROM USFDA BEFORE THE TESTING STARTS?
There is no need to file any documents or obtain any pre-approval from the USFDA prior to BCS biowaiver testing.
WHAT ARE THE CHANCES THAT 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.

DO WE NEED TO PROVIDE CLINICAL DATA AS SUPPORT?
Clinical data is only required as support if the Sponsor opts not to perform specific sections of the in vitro study. For example, if the stability of the compound in simulated gastric and intestinal fluids is not evaluated to show that drug loss from the gastrointestinal tract is due to intestinal membrane permeation rather than degradation, clinical data indicating that the extent of absorption is $\geq 90\%$ is required as support.

ARE THERE ANY SPECIFIC FORMS OR MODULES REQUIRED FOR SUBMISSION OF A BCS WAIVER?
Summary tables in module 2.7 should include data generated from the solubility, permeability and dissolution studies. Additional information on establishing equivalence and analytical methods may be incorporated in module 5.

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.
Global Standards

WHY ARE MY COLLEAGUES OUTSIDE THE US NOT FAMILIAR WITH THIS APPROACH? DOES IT MEAN THAT THEY HAVE ALREADY CONSIDERED AND REJECTED THE IDEA?

The USFDA issued a Guidance on BCS biowaivers in 2000. Since then, Absorption Systems has classified over 100 unique compounds using a validated test system. Eight of the ten largest generic companies have conducted BCS biowaiver studies with Absorption Systems. The number of studies performed annually continues to increase as acceptance of this regulatory pathway has become more widespread.

OUR BE STUDY IS PART OF A PRODUCT REGISTRATION DOSSIER THAT IS SUBMITTED TO MULTIPLE COUNTRIES. IF A BCS BIOWAIVER IS ADMISSIBLE ONLY IN THE US, WILL I STILL NEED TO RUN A BE STUDY TO SATISFY THE REQUIREMENTS OF OTHER COUNTRIES?

Biowaivers are accepted by many countries, and efforts toward international harmonization are greater than ever. Biowaivers can be filed as soon as dissolution, solubility, and permeability tests are completed – enabling early access to these markets.

WHAT ARE THE MAIN DIFFERENCES BETWEEN USFDA AND OTHER DRUG REGULATORY AGENCIES?

There are some differences among regulatory agencies with regard to BCS biowaiver eligibility, although they are largely similar. Standard criteria are summarized in the table on page 13.

China Taipei, Mexico, and Japan do not grant BCS-based biowaivers at present. China, Singapore/ASEAN, South Korea, and USA grant biowaivers for BCS class I drugs. EMA, Health Canada, and WHO will consider biowaivers for both BCS class I and class III drugs (Davit et al., 2013).
<table>
<thead>
<tr>
<th>Country</th>
<th>Year Issued</th>
<th>Dissolution</th>
<th>Permeability</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>2000</td>
<td>85% in 30 min</td>
<td>90%</td>
<td>1-7.5</td>
</tr>
<tr>
<td>Europe</td>
<td>2001 (2010)</td>
<td>85% in 30 min</td>
<td>85%</td>
<td>1-6.8</td>
</tr>
<tr>
<td>ASEAN</td>
<td>2004</td>
<td>Rapid</td>
<td>High</td>
<td>1-6.8</td>
</tr>
<tr>
<td>WHO</td>
<td>2006</td>
<td>85% in 30 min</td>
<td>85%</td>
<td>1.2-6.8</td>
</tr>
<tr>
<td>ANVISA</td>
<td>2011</td>
<td>Specified List</td>
<td>85%</td>
<td>Specified List</td>
</tr>
<tr>
<td>TGA</td>
<td>2011</td>
<td>85% in 15 min</td>
<td>85%</td>
<td>1-6.8</td>
</tr>
<tr>
<td>Canada*</td>
<td>2012</td>
<td>85% in 30 min</td>
<td>85%</td>
<td>1.2-6.8</td>
</tr>
</tbody>
</table>

* Draft.

Source: Malins et al., May 2012
References


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