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Review Article

Theme: Leveraging BCS Classification and in-silico Modeling for Product Development
Guest Editors: Divyakant Desai, John Crison, and Peter Timmins

Biopharmaceutics Classification System-Based Biowaivers for Generic Oncology Drug Products: Case Studies

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Abstract. Establishing bioequivalence (BE) of drugs indicated to treat cancer poses special challenges. For ethical reasons, often, the studies need to be conducted in cancer patients rather than in healthy volunteers, especially when the drug is cytotoxic. The Biopharmaceutics Classification System (BCS) introduced by Amidon (1) and adopted by the FDA, presents opportunities to avoid conducting the bioequivalence studies in humans. This paper analyzes the application of the BCS approach by the generic pharmaceutical industry and the FDA to oncology drug products. To date, the FDA has granted BCS-based biowaivers for several drug products involving at least four different drug substances, used to treat cancer. Compared to *in vivo* BE studies, development of data to justify BCS waivers is considered somewhat easier, faster, and more cost effective. However, the FDA experience shows that the approval times for applications containing *in vitro* studies to support the BCS-based biowaivers are often as long as the applications containing *in vivo* BE studies, primarily because of inadequate information in the submissions. This paper deliberates some common causes for the delays in the approval of applications requesting BCS-based biowaivers for oncology drug products. Scientific considerations of conducting a non-BCS-based *in vivo* BE study for generic oncology drug products are also discussed. It is hoped that the information provided in our study would help the applicants to improve the quality of ANDA submissions in the future.

KEY WORDS: Biopharmaceutics Classification System; bioequivalence; biowaiver; cancer; oncology.

INTRODUCTION

For two drug products to be bioequivalent, the active drug ingredient or the active moiety in the test product must exhibit the same rate and extent of absorption as the reference drug product (21 CFR 320.1(e) and 320.23(b)). Demonstrating bioequivalence (BE) *in vivo* in humans is the most preferred method of ensuring the therapeutic equivalence of generic drug products to the reference listed drug (RLD) product. The *in vivo* BE studies need to be carefully designed based on biopharmaceutical, ethical, clinical, pharmacokinetic, analytical, and statistical considerations. On a practical level, it is often difficult to enroll patients for an *in vivo* study due to the problem of identifying demographically matching patients such as in less frequent or rapidly progressing cancers. Alternate approaches provided by regulations, including *in vitro* testing are applicable to demonstrate BE.

The FDA has utilized the scientific principles of the Biopharmaceutics Classification System (BCS) as one of the regulatory tools to grant biowaivers for solid oral immediate release (IR) drug products through *in vitro* tests. The rationale for this approach is that three main factors, namely, the solubility and permeability of a drug substance, and dissolution rate of a drug product, govern the rate and extent of oral drug products at the absorption site. The class I category of the Biopharmaceutics Classification System includes drugs that have high aqueous solubility and high intestinal membrane permeability. Thus, if the products containing BCS class I drugs are formulated to dissolve rapidly in relation to the gastric emptying and do not contain excipients that are known to affect absorption or the gastrointestinal transit time of the drug substance, then BE of these formulations can be considered self-evident and the need for *in vivo* studies can be waived.

The FDA began implementation of the BCS paradigm as a regulatory tool in 1995, when the Guidance for Scale Up and Post Approval Changes (SUPAC) for immediate release (IR) products was issued (2). In this guidance, the agency introduced the regulatory definition of a highly soluble and highly permeable drug substance. From 1995–2000, biowaivers were limited to the approvals of supplements for scale up and other

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manufacturing changes of approved drug products. In August 2000, the FDA issued the BCS guidance (3) and extended the regulatory considerations for granting biowaivers for approval of drug products if the application was for an IR oral drug product containing a BCS class I drug substance. In this guidance, the agency further clarified the definition of a highly permeable drug substance.

For products containing BCS class I drugs, the Office of Generic Drugs (OGD) encourages the applicants to request a waiver of *in vivo* BE studies with appropriate documentation regarding high solubility and high permeability of the drug substances, along with their stability in the gastrointestinal tract, and rapid dissolution of the drug products, as detailed in the BCS guidance (3). The OGD has reviewed and approved requests for BCS-based biowaivers for several multisource oncology drug products. For oncology drug products, more so than products of some other classes of drugs, the BCS-based biowaiver approach provides many advantages considering the complexities involved in conducting the *in vivo* BE studies. This is especially true for oncology drugs that are also cytotoxic. Frequently, it is considered unethical to perform studies in healthy volunteers using these cytotoxic drugs. Also, under 21 CFR 320.31, it would require the generic product developers to submit an investigational new drug (IND) application (also called Bio-IND) for review, prior to conducting the BE studies. If the design of the human study is unsafe, the OGD may impose a clinical hold for safety reasons following the review of the Bio-IND. The studies for oncology drug products often need to be managed at multiple clinical sites to recruit sufficient number of patients. Higher inter- and intra-subject variability, management of relatively larger number of adverse events and even deaths are expected in these studies.

This paper provides the OGD's regulatory experience of the application of biowaivers for BCS class I drug products, in particular, the oncology drug products. Issues that delayed the approvals are discussed for this drug class. Besides the obvious advantages of the savings in the cost and time for drug development, granting BCS-based biowaivers are expected to reduce the regulatory burden by reducing the review cycles and shortening the drug approval times. However, many applicants seem to be missing out on these opportunities. It is hoped that bringing some of the commonly occurring issues to the forefront will hasten approvals of this important class of drugs and ensure that therapeutically equivalent, generic oncology drug products are available to the patients at reduced cost and in a timely manner.

METHODS

A survey of the New Drug Applications (NDAs) and the Abbreviated New Drug Applications (ANDAs) submitted to the agency in the past 10 years, which included requests for BCS I waivers, has been conducted for this paper. These applications encompass drugs used to treat a wide range of indications including, seizures, cancer, anxiety disorders, dementia, nausea, vomiting, pain, etc. Through our survey, we identified the oncology drug products containing at least four different drug substances that were considered eligible for BCS-based biowaiver by the Center for Drug Evaluation and Research (CDER), based on the review of the data of BCS I evidence. We identified an additional drug substance used to treat cancer, for which the generic drug applicant has requested a BCS-based biowaiver; however, due to insufficient information, the eligibility for a biowaiver for this application has not been concluded. For generic products of these five drug substances, some ANDAs were BCS-based while others were based on traditional *in vivo* BE studies conducted in humans (i.e., non-BCS-based). We assessed the number of review cycles undergone for each of these applications, identified the common deficiencies associated with the studies in these applications, and compared the review process between BCS-based and non-BCS-based ANDAs.

RESULTS AND DISCUSSION

The CDER has evaluated the data for 55 drug substances formulated as IR solid oral dosage forms and has considered the products containing 41 of the 55 drug substances as eligible for the BCS-based biowaiver, based on the data submitted in the applications. Four of the mentioned 41 drug substances (~10%) are indicated to treat cancer. In contrast, the WHO's essential medicines list (4) includes 21 drugs under the BCS class I category and only one of these is indicated for cancer treatment.

To date, the OGD has received *49* ANDAs for the *4* oncology drugs identified through our survey. Among these *49* applications, 30 ANDAs (60%) contained data from *in vivo* BE studies to show equivalent pharmacokinetic metrics for the generic and reference products under the fasted or fed conditions. For the other *19* ANDAs (40%), the applicants pursued the BCS-based biowaiver approach, primarily through submission of data from three types of *in vitro* testing: permeability, solubility, and dissolution.

If the ANDA applicants, in their original submission, provide adequate information and scientifically sound evidence to support the bioequivalence of the generic product, such applications would generally be found acceptable by the agency, with respect to bioequivalence requirements, in one review cycle. However, if the submissions do not contain sufficient information, or data do not adequately support the claim of bioequivalence, the agency would issue deficiency comments to the applicants and request more information. This results in more review cycles and delay in the approval of the applications.

For those 30 applications containing *in vivo* BE studies, 23 ANDAs have been reviewed and 11 of these 23 ANDAs have acceptable bioequivalence studies that needed only one cycle of bioequivalence review. This constitutes nearly one half (48%) of the total applications in this category that were evaluated by the OGD. In contrast, for the *19* applications containing *in vitro* BCS-related studies and requests for BCS-based biowaivers, 11 ANDAs have been reviewed and only one ANDA (9% of total applications that were reviewed) included complete and appropriate BCS-related information enabling the completion of the review of the BE portion in one review cycle. The other 10 ANDAs have undergone between two to five review cycles.

Part of the reasons why the majority of BCS-based biowaiver submissions had longer review periods (i.e., less than 10% found adequate in the first review cycle) compared to applications containing *in vivo* BE studies (i.e., 48% found adequate in the first review cycle) can be found in the case studies discussed below. Each of the case studies refers to a

different drug substance. The major issues identified during the review of the different ANDAs are highlighted in the case studies below.

Case study 1 The applicant requested a biowaiver for an oncology drug product based on the BCS I approach. The parent drug substance is a prodrug that is converted *in vivo* to its active metabolites. Its permeability may therefore be influenced by the mechanism and site (anatomical) of conversion to the active metabolites. Since, the information about how and where this drug is metabolized is lacking, the agency could not grant the BCS waiver request based on the *in vitro* testing data of the parent drug substance alone. The FDA's BCS guidance (3) describes the additional considerations for *in vitro* testing on the prodrugs and active metabolites. Accordingly, the agency requested the applicant to submit *in vitro* testing data on all the active metabolites of the prodrug.

Case study 2 In this case, the applicant requested a BCS-based biowaiver for a generic drug product containing a cytotoxic agent. The applicant submitted *in vitro* dissolution testing data alone to support the waiver request. To support its assertion of high solubility and high permeability of the drug substance, the applicant referenced published literature and did not conduct solubility and permeability testing. The agency currently does not accept published literature as pivotal evidence for a BCS-based biowaiver request. Peer reviewed articles may not contain the necessary details of the testing for the agency to make a judgment regarding the quality of studies, and the agency does not have the ability to verify the peer reviewed articles. Therefore, the applicant was recommended to provide appropriate data for the solubility and permeability tests, as detailed in the CDER Guidance to Industry (3).

Case study 3 The applicant cited the labeling information of the RLD product as the evidence of high permeability and submitted *in vitro* evidence to support high solubility of the drug substance and rapid dissolution of the drug product. The data for stability testing showed that the drug substance was not stable at certain pH conditions in the gastrointestinal tract. For the purpose of the BCS-based biowaiver, the FDA considers a drug substance to be highly permeable if its absorption in humans is at least 90%, provided that the *in vitro* data support the stability of the drug substance in the gastrointestinal tract. However, in the original submission, the applicant did not provide a scientific justification for why the drug product was eligible for a BCS-based biowaiver, despite the observed gastrointestinal instability at a certain pH level.

Similarly, to qualify for a BCS-based biowaiver, the agency evaluates whether the drug product would dissolve rapidly in different pH milieu across the gastrointestinal tract. In this case, the data for dissolution testing in multiple media (0.1 N HCl, 4.5 pH buffer, and 6.8 pH buffer) using the applicant's proposed method showed that the drug product dissolved rapidly at some pHs but not at all pHs. In addition, some strengths but not all strengths of the drug product showed incomplete release at a lower rotation speed due to the coning effect caused by the excipient in the formulation of the drug product. At the agency's request, the applicant later developed a more appropriate method using the USP apparatus recommended in the Guidance (3) to show rapid dissolution of the drug product.

Besides the major flaws discussed above in the case studies, additional commonly seen deficiencies identified in these case studies are also identified. These issues are primarily related to the inadequacy and incompleteness of the submission and can be easily avoided if greater attention is paid. These deficiencies are summarized in Table I, classified by the types of studies.

The above three cases present some of the recurring issues associated with ANDA applications submitted with BCS-based biowaiver requests.

While the issues identified in these case studies are based on the review of applications for oncology drug products included in the survey, OGD experience has shown that the issues are not specific *to this therapeutic class* and are applicable in general to the *in vitro* permeability, solubility, and dissolution testing for generic drug applications requesting a waiver of the *in vivo* BE requirements based on the BCS class I designation. The issues identified are also not unique to the drug substance. The majority of the time delay in approval is related to the poor quality of the data (high variability, inadequate replicates), inappropriate test methods, and lack of supporting information for the conduct of the studies, such as the method validation reports for the solubility, permeability, and dissolution tests, as well as the analytical method used to quantitate the drug substance or the active metabolites.

In addition, the case studies described above highlight some of the considerations when deciding to pursue the BCS-based biowaiver option to establish bioequivalence. For example, for a prodrug, depending on whether the site of conversion of prodrug is prior to or after intestinal permeation, *in vitro* permeability testing maybe needed on the metabolites. Solubility data on both prodrug and drug can be relevant as well. Including this information with the original submission should avoid having to amend the applications. Similarly, when the data do not support the stability of the drug substance or rapid dissolution of the drug product at all pH conditions, or passive diffusion of the drug substance across the permeable membrane, the applicant should consider the scientific basis, for why the ANDA should still be considered for a BCS-based biowaiver.

In contrast, the challenges for applicants pursuing the *in vivo* BE approach for oncology drugs are driven mainly by the design and conduct of the clinical studies. Because of the cytotoxicity and other serious toxicities, the *in vivo* BE studies for oncology drugs are generally conducted in the target patient population rather than in healthy volunteers. Several aspects of the study protocol need to be addressed to ensure the adequacy of the study design and the safety of the study subjects. For cytotoxic drugs, the FDA regulations require that applicants submit a Bio-IND prior to initiating the BE studies in humans. The Agency reviews the study

Table I. Summary of Additional Common Deficiencies Observed for the above Case Studies

Type of study	Commonly seen deficiencies	Examples
Permeability study	Missing information to support the validity of the study	Permeability data for the model drugs were missing. Validation report for the analytical methods and the relevant method SOPs were not submitted.
	Insufficient number of replicates to allow for the statistical assessment of the variability in the study data	
Solubility study	Missing information to support the validity of the study	Information to indicate if the pH of the medium was verified after addition of the drug substance to the buffer medium was missing. Validation report for the analytical methods and the relevant method SOPs were not submitted.
	Missing information for the reported data	Information for the precision of the reported data was missing.
	Inadequate study design	Data were not collected under equilibrium condition. Data were not collected using a stability indicating assay.
Dissolution study	Missing information	A description of the dissolution method parameters such as volume, speed, and apparatus type was missing. Validation report for the analytical methods and the relevant method SOPs were not submitted.

protocols submitted in the Bio-IND and provides guidance and comments. The agency also provides comments and guidance on the protocols submitted for non-cytotoxic drugs. For drug substances identified in case studies 2 and 3, the agency has reviewed several protocols some of which were submitted in the Bio-INDs and provided guidance on the critical aspects of the study protocols including the following:

Subject selection Due to serious toxicity of the drug substances, the studies were recommended in patients. The targeted patient population was limited to the treatment indications described in the labeling of the innovator's drug. Due to difficulty in recruiting targeted patients only, it was acceptable for the applicants to conduct the studies at multiple clinical facilities and in multiple groups.

Dose selection Modifying or discontinuing the patient's therapeutic dosing regimen for the sake of patients' participation in the studies is unethical; therefore, the doses recommended for the studies were specific to the patient's individual dosing regimen. Dose-normalization was not recommended; however, patient selection was recommended to be within a dosing range limit. Each patient was to receive the same dose in all study periods to avoid difficulties in interpretation of the study data.

Dosing regimen, sampling time, and washout period The guidelines for therapy described in the drug label were considered in making recommendations for the dosing regimen while the pharmacokinetic parameters such as the elimination rates and the half-lives of the drugs were considered in ensuring the adequacy of the sampling times and washout periods.

Fasted or fed conditions These recommendations were based on the description in the RLD label. As a general rule, the OGD recommends BE studies under the fasting and fed conditions. However, sometimes, the safety issues preclude conducting studies under both conditions. For oncology drugs, patients are expected to have concomitant diseases like hypertension, diabetes mellitus, or hypercholesterolemia. Subjecting such patients to consume a high fat meal would not be safe or ethical. Anorexic patients may not consume the entire meal leading to difficulties in interpretation of data across the sites. Therefore, the OGD concurred with the use of modified meals for the studies.

Coadministration of drugs Recommendation against co-administration of certain non-study medication was made, by considering the pharmacology and pharmacokinetics of the non-study medication to decrease the clearance of the study drugs and the likelihood of a drug-drug interaction.

Statistical considerations If the studies would be conducted at multiple sites and in multiple groups, testing for these variables in the statistical model was recommended.

A likely reason for the relatively fewer deficiencies for the non-BCS-based ANDAs compared to BCS-based ANDAs described above, could be the recommendations from the agency, following the review of the Bio-INDs and prior to conducting the studies. We surveyed the deficiencies identified in the reviews of the *in vivo* studies for the applications containing the same drug substance as in the case studies above. For the drug substance associated with case study 1, no *in vivo* BE studies have been submitted in the ANDAs. The OGD has reviewed at least five ANDAs that included data from *in vivo* BE studies for the drug substances associated

with case studies 2 and 3. For two of the five ANDAs, the BE studies were acceptable in the first review cycle. For the other three ANDAs, the deficiencies were minor and related to the missing information in the bioanalytical report of two ANDAs and the clinical report of one ANDA.

Although our experience shows that the BE studies for majority of the non BCS-based ANDAs were found adequate in one review cycle suggesting shorter approval times of these ANDAs, the time associated with the submissions of the Bio-INDs prior to the submission of the ANDAs also needs to be considered.

CONCLUSION

The BCS-based option presents opportunities to avoid exposing humans to clinical trials. It may be possible to request BCS-based biowaivers of *in vivo* testing for solid oral drug products formulated for immediate-release, provided that the drug substance and the drug product meet certain criteria described in the guidance. The agency can make a decision regarding the acceptability of the waiver request only upon review of the data submitted in the application. The FDA's guidance for the industry on BCS is aimed to help the applicants who wish to request a waiver of *in vivo* bioavailability and/or bioequivalence studies for immediate release solid oral dosage forms. It is our hope that many of the issues identified in the case studies above will be avoided in the future, by conducting studies in accordance with the criteria set forth in the guidance and providing a complete and high quality submission.

Disclosure This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

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