



6 WEST HUBBARD STREET  
SUITE 500  
CHICAGO, IL 60610  
www.rmmslegal.com

312-527-2157 main phone  
312-527-4205 main fax

**William A. Rakoczy**  
312.222.6301 telephone  
312.222.6321 facsimile  
wrakoczy@rmmslegal.com

November 9, 2007

**VIA MESSENGER**

Division of Dockets Management  
Food and Drug Administration  
Department of Human and Health Services  
Room 1061  
5630 Fishers Lane  
Rockville, MD 20852

3074 7 NOV -9 11:44

**CITIZEN PETITION**

On behalf of Cobalt Laboratories Inc. and Cobalt Pharmaceuticals Inc. (collectively, "Cobalt"), the undersigned hereby submits this Citizen Petition, in quadruplicate, pursuant to 21 U.S.C. § 355(j) of the Federal Food, Drug, and Cosmetic Act, as well as 21 C.F.R. § 10.20, § 10.30, and § 320.1 *et seq.*

**A. ACTION REQUESTED**

Petitioner Cobalt respectfully requests that the Office of Generic Drugs of the U.S. Food and Drug Administration ("FDA") make the determination that no abbreviated new drug application ("ANDA") submitted under 21 U.S.C. § 355(j) and referencing Bayer's NDA No. 20-482 for Precose® (acarbose) shall be granted final agency approval unless and until such an ANDA contains sufficient evidence data to establish bioequivalency in accordance with 21

2007P-0448

CP1

U.S.C. § 355(j), 21 C.F.R. § 320.21, and 21 C.F.R. § 320.23. Specifically, Petitioner requests that FDA:

1. require all applicants submitting an ANDA referencing Bayer's NDA No. 20-482 for Precose® (acarbose) to conduct the required *in vivo* bioequivalence tests and studies comparing the proposed generic product to Precose®, the reference listed drug;
2. refrain from granting any *in vivo* bioequivalence waiver for any ANDA referencing Bayer's NDA No. 20-482 for Precose® (acarbose); and
3. require that the results of such tests and studies establish the *in vivo* bioequivalence of any generic Precose® product sufficient to permit final approval of any such ANDA pursuant to 21 U.S.C. § 355(j)(8)(A)(ii) and 21 C.F.R. § 320.21.

#### **B. STATEMENT OF GROUNDS**

An ANDA applicant must establish, *inter alia*, that its proposed drug product is "bioequivalent" to the reference listed drug ("RLD"). See 21 U.S.C. § 355(j)(2)(A)(iv).<sup>1</sup> Demonstrating bioequivalence to the RLD referenced in the application is, in fact, critical to obtaining FDA approval: "A major premise underlying the [Hatch-Waxman Amendments] is that bioequivalent drug products are therapeutically equivalent, and therefore, interchangeable."

---

<sup>1</sup> A generic drug product is "bioequivalent" when:

(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

(ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

(FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations*, p. vii (27th ed. 2007)).

**I. Acarbose ANDA Applicants Cannot Obtain An *In Vivo* Bioequivalence Waiver Under FDA's Regulations.**

In most instances, an ANDA applicant must demonstrate *in vivo* bioequivalence (BE) of its generic product to the RLD. In certain limited instances, an ANDA applicant may request a biowaiver, which eliminates the requirement that an applicant submit evidence demonstrating the *in vivo* bioequivalence of its generic drug product to the RLD. See 21 C.F.R. §§ 320.21(b)(2) and 320.22(a). For solid, oral dosage forms, FDA may grant a biowaiver to an ANDA applicant only in the following circumstances:

FDA shall waive the requirement for the submission of evidence measuring the *in vivo* bioavailability or demonstrating the *in vivo* bioequivalence of a solid oral dosage form (other than a delayed release or extended release dosage form) of a drug product determined to be effective for at least one indication in a Drug Efficacy Study Implementation [DESI] notice or which is identical, related, or similar to such a drug product under § 310.6 of this chapter unless FDA has evaluated the drug product under the criteria set forth in § 320.33, included the drug product in the Approved Drug Products with Therapeutic Equivalence Evaluations List, and rated the drug product as having a known or potential bioequivalence problem. A drug product so rated reflects a determination by FDA that an *in vivo* bioequivalence study is required.

21 C.F.R. § 320.22(c). Precose®, approved in 1995, has not been the subject of a DESI notice, nor is it “identical, related, or similar to such a drug product under [21 C.F.R.] § 310.6.” Consequently, this regulation does not provide any legal basis for granting a biowaiver of *in vivo*

bioequivalence requirements to an ANDA applicant seeking FDA approval to market a generic acarbose product.<sup>2</sup>

**II. Acarbose ANDA Applicants Cannot Obtain A Bioequivalence Waiver Under FDA's *Guidance For Industry*.**

**A. Criteria For Receiving A Biowaiver Under FDA's Guidance.**

FDA has issued a *Guidance for Industry* concerning the waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms. (See *Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (Aug. 2000) ("*Biowaiver Guidance*"). The *Biowaiver Guidance* discusses FDA's Biopharmaceutics Classification System ("BCS") for immediate-release ("IR") solid oral dosage form drug products. The BCS groups IR solid oral dosage forms into one of four categories, based on the aqueous solubility and intestinal permeability of the drug substance:

- Class 1: High Solubility – High Permeability
- Class 2: Low Solubility – High Permeability
- Class 3: High Solubility – Low Permeability
- Class 4: Low Solubility – Low Permeability

(*Biowaiver Guidance* at 1-2). Additionally, the drug substance is classified as having either rapid or slow dissolution properties. (*Id.* at 2). If an IR drug substance qualifies as a Class 1 drug substance (*i.e.*, it has high aqueous solubility and high intestinal permeability) and has rapid dissolution properties, it may be eligible for a biowaiver under 21 C.F.R. § 320.22(e). (*Id.*).

---

<sup>2</sup> The biowaiver provisions of 21 C.F.R. § 320.22(b) do not apply to solid, oral dosage forms. Further, § 320.22(d) permits a biowaiver for different strength products where the specified criteria are satisfied; where an application contains evidence that the drug product is "shown to meet an *in vitro* test that has been correlated with *in vivo* data"; or to a reformulated product that contains different color, flavor, or preservatives where the specified criteria are met. 21 C.F.R. § 320.22(d). It thus is inapplicable here.

Otherwise, it is not eligible and FDA has no discretion to waive *in vivo* bioequivalence requirements.

The *Biowaiver Guidance* contains standards by which to evaluate and identify the solubility and permeability classification of an IR solid oral dosage form of a drug.

The solubility class boundary is based on the highest dose strength of an IR drug substance. (*Id.*). According to FDA, a drug substance is considered “highly soluble” when “the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5.” (*Id.*; *see also id.* at 3).

The permeability class boundary is based on the extent a drug substance is absorbed in humans. “In the absence of evidence suggesting instability in the gastrointestinal tract,” a drug substance is considered “highly permeable” when “the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.” (*Id.*; *see also id.* at 4-7). Several different methods can be used to determine the gastric permeability of an IR drug substance under the BCS guidelines. Pharmacokinetic mass balance studies using radiolabeled or unlabeled, stable isotopes of a drug substance “can be used to document the extent of absorption of a drug.” (*Id.* at 4). Oral bioavailability studies, using an intravenously-administered reference, also can be used to verify absorption of a drug substance. If pharmacokinetic studies in humans are insufficient, however, additional tests may be used to determine the permeability of a drug substance from the gastrointestinal tract. These include: “(1) *in vivo* intestinal perfusion studies in humans; (2) *in vivo* or *in situ* intestinal perfusion studies using suitable animal models; (3) *in vitro* permeation studies using excised human or

animal intestinal tissues; or (4) in vitro permeation studies across a monolayer of cultured epithelial cells.” (*Id.*).

**B. Acarbose Does Not Satisfy The Criteria For Receiving A Biowaiver Under FDA’s Guidance.**

Bayer currently sells acarbose under the trade name Precose® in the United States as 25, 50, and 100 mg tablets. Bayer sells acarbose in Europe under the name Glucobay™ as 50 and 100 mg tablets, and in Canada under the name Prandose® as 50 and 100 mg tablets. The Glucobay™ product monograph contains a more thorough listing of physical and pharmacokinetic data than the prescribing information for Precose® and has been used to evaluate acarbose in view of the *Biowaiver Guidance* and BCS guidelines found therein.

**1. Scientific Literature On Acarbose.**

Bayer published the most recent product monograph for Glucobay™ in May 2006. The product monograph discloses the action and clinical pharmacology of acarbose, indications and clinical use of acarbose, contraindications thereof, interactions of acarbose with other drugs, adverse reactions of patients to acarbose in clinical studies, dosage and administration of acarbose, pharmaceutical information regarding acarbose, and information for the patient. The product monograph describes acarbose as having solubility in water of approximately 140 g/100 mL at 20° C. (*See* Product Monograph for Glucobay™ (Acarbose Tablets) at 16 (May 30, 2006), Exhibit A hereto). In addition, it states that acarbose is absorbed from an oral dose as 1-2% active drug, while 51% is excreted in the feces as unabsorbed radiolabeled acarbose. (*See id.* at 3). And “89% of the dose was recovered in the urine as active drug within 48 hours” when acarbose was given intravenously. (*Id.* at 4).

Several reports have published studies on the pharmacokinetics of acarbose. Comparison of areas under the plasma concentration-time curves ("AUC") after oral administration with those resulting from intravenous administration showed the acarbose from oral dosing has only about 0.6% systemic availability of the unchanged drug as compared to the intravenous dose. (See J. Puetter, *Studies on the Pharmacokinetics of Acarbose in Humans*, in ENZYME INHIBITORS 139, 149 (U. Brodbeck ed., 1980), Exhibit B hereto). A later study reported a systemic availability of 1.58% after oral dosage compared to the same dose administered intravenously. (See J. Pütter et al., *Pharmacokinetics of acarbose*, in PROCEEDINGS OF FIRST INTERNATIONAL SYMPOSIUM ON ACARBOSE 38, 45 (W. Creutzfeldt ed., 1982), Exhibit C hereto). A summary of pharmacokinetic data was published in 1988. (See Stephen P. Clissold & Clive Edwards, *Acarbose: A Preliminary Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential*, 35 DRUGS 214, 225-26 (1988), Exhibit D hereto).

Additional studies examined the pharmacokinetics (absorption, metabolism, excretion) of acarbose in humans, rats, and dogs via oral and intravenous administration (IV) (intraduodenal administration was also tested in rats) of radiolabeled acarbose. After IV administration, "the radioactivity was excreted renally almost completely (~94% of the dose) in all species investigated." (See H.J. Ahr et al., *Pharmacokinetics of Acarbose*, 39 ARZNEIM.-FORSCH./DRUG RES. 1254, 1256 (1989), Exhibit E hereto). After oral administration, the majority of acarbose was excreted in feces (80% in rats and in dogs, 51% in humans), with renal excretion 14.5% in rats, 8% in dogs, and 35% in humans. (*Id.*). In rats who were administered acarbose via the bile duct (intraduodenally), only 15.9% was absorbed as determined by urine excretion analysis. (*Id.* at 1256-57). The amount of unchanged acarbose excreted was 0.3% in

rats, 3.4% in dogs, and 1.7% in humans. (*Id.* at 1257). This is indicative of a very low absorption for unchanged acarbose. (*Id.* at 1257). AUC studies measured from plasma levels were also undertaken. AUC values for unchanged acarbose after oral administration was only 1.4% that of the value recorded after intravenous administration in healthy male volunteers. (*Id.* at 1258).

A later study reported results of mass balance studies with radiolabeled <sup>14</sup>C-acarbose. "Urinary excretion data suggest[ed] that approximately 35% of a dose was absorbed," but most of the radiolabeled carbon was excreted as metabolites. (See Julia A. Balfour & Donna McTavish, *Acarbose: An Update of its Pharmacology and Therapeutic Use in Diabetes Mellitus*, 46 DRUGS 1025, 1037 (1993), Exhibit F hereto). Moreover, approximately 50% of the radiolabeled acarbose was recovered in feces. (*Id.*).

## **2. Acarbose Does Not Qualify For An *In Vivo* Bioequivalence Waiver.**

As reported in the product monograph, the solubility of acarbose in water is 140 g/100 mL at 20° C. As 100 mg is a significantly smaller amount than the 140 g capable of dissolving in 100 mL of water, the highest dose strength of acarbose would dissolve in 250 mL of water. Therefore, acarbose could possibly meet the description of a "highly soluble drug substance," as set forth in the *Biowaiver Guidance*. Significantly, however, the mass balance studies do not establish acarbose as a "high permeability drug," as set forth in the *Biowaiver Guidance*. Quite the contrary, all available data and information suggests that acarbose is a low, not high, permeability drug.

Each of the mass balance studies reported approximately 35% of radiolabeled carbon collected in urine. This indicates 35% of the total dose was permeable through the

intestine, but mostly as metabolites. Further, the same reports recorded about 50% of radiolabeled carbon collected in fecal matter as part of unchanged acarbose. Excretion of the drug substance in feces indicated it never permeated the gastrointestinal tract. Therefore, it is not possible for 90% or more of an acarbose dose to be permeable through the intestine, as required by the *Biowaiver Guidance*. After intravenous administration of a dose of acarbose, 89-94% of the dose was recovered as the active drug in urine. But AUC values after oral administration were only approximately 0.7-2.0% as compared to after intravenous administration. In other words, the mean systemic availability of unchanged acarbose after oral administration is only 0.7-2.0%, far below 90% of the administered dose. These AUC studies further support the conclusion that acarbose is a low permeability drug.

Consequently, as evaluated by the reported scientific data, in view of the BCS guidelines, acarbose is at best a highly soluble, low permeable drug substance. Therefore, acarbose is categorized as a Class 3 drug, rather than a Class 1 drug, rendering it ineligible for a biowaiver of *in vivo* bioequivalence studies. Any ANDA applicant seeking approval of a generic acarbose product therefore must conduct *in vivo* bioequivalence studies, and may not seek or qualify for a biowaiver.<sup>3</sup>

#### IV. Conclusion.

For the reasons cited above, Petitioner requests that FDA:

---

<sup>3</sup> An IR drug product is considered "rapidly dissolving" when "no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using *U.S. Pharmacopeia* (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes." (*Biowaiver Guidance* at 2-3; *see also id.* at 7-8). The available scientific literature does not establish that acarbose is rapidly dissolving, within *Biowaiver Guidance* definition. Even if acarbose were "rapidly dissolving," it nevertheless is ineligible for a biowaiver because it is a Class 3 drug.

1. require all applicants submitting an ANDA referencing Bayer's NDA No. 20-482 for Precose® (acarbose) to conduct the required *in vivo* bioequivalence tests and studies comparing the proposed generic product to Precose®, the reference listed drug;
2. refrain from granting any bioequivalence waiver for any ANDA referencing Bayer's NDA No. 20-482 for Precose® (acarbose); and
3. require that the results of such tests and studies establish the *in vivo* bioequivalence of any generic Precose® product sufficient to permit final approval of any such ANDA pursuant to 21 U.S.C. § 355(j)(8)(A)(ii) and 21 C.F.R. § 320.21.

**C. ENVIRONMENTAL IMPACT**

Under 21 C.F.R. § 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

**D. ECONOMIC IMPACT**

According to 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

**E. CERTIFICATION**

Pursuant to 21 C.F.R. § 10.30(b), the undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition. Pursuant to 21 U.S.C. § 355(q)(1)(H), I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were

Division of Dockets Management  
November 9, 2007  
Page 11

disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: October 2007. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Cobalt. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Very truly yours,

RAKOCZY MOLINO MAZZOCHI SIWIK LLP



William A. Rakoczy

*Counsel for Cobalt Laboratories Inc. and Cobalt  
Pharmaceuticals Inc.*

Enclosures

cc: Dawn Beto, Cobalt Laboratories Inc.