IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

VIROPHARMA INCORPORATED,
730 Stockton Drive, Exton, PA 19341,

Plaintiff,

v.

MARGARET A. HAMBURG, M.D., in her official capacity as COMMISSIONER, FOOD AND DRUG ADMINISTRATION, and FOOD and DRUG ADMINISTRATION, 10903 New Hampshire Ave., Silver Spring, MD 20903;

KATHLEEN SEBELIUS, in her official capacity as SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES, and DEPARTMENT OF HEALTH AND HUMAN SERVICES, 200 Independence Avenue, S.W., Washington, D.C. 20201,

Defendants.

Case: 1:10-cv-01529
Assigned To : Friedman, Paul L.
Assign. Date : 9/10/2010
Description: General Civil

The Honorable _____

VIROPHARMA INCORPORATED'S COMPLAINT FOR DECLARATORY RELIEF

Plaintiff ViroPharma Incorporated ("ViroPharma") brings this action for declaratory relief against the Food and Drug Administration ("FDA"), Margaret A. Hamburg, M.D., in her official capacity as Commissioner of FDA, the United States Department of Health and Human Services ("HHS"), and Kathleen Sebelius, in her official capacity as Secretary of HHS, (collectively "FDA" or "Defendants"). In support thereof, ViroPharma states the following:

NATURE OF THE ACTION

1. This action complains of FDA's failure to conduct notice-and-comment rulemaking prior to amending its bioequivalence regulations.

2. ViroPharma seeks review under the Administrative Procedure Act of the FDA's decision to change its regulations to abandon its longstanding rule that applicants for an Abbreviated New Drug Application ("ANDA") seeking waiver of the requirement of 21 C.F.R. § 320.21 (2010) (*i.e.*, that bioequivalence must be demonstrated by *in vivo* evidence) must satisfy one of the enumerated waiver criteria of 21 C.F.R. § 320.22.

3. FDA effectively amended its regulations in its May 7, 2008 response to a Citizen Petition regarding the drug Precose (acarbose) filed by Cobalt Laboratories Inc. and Cobalt Pharmaceuticals, Inc. (collectively "Cobalt"). In that response, FDA determined that the bioequivalence methods listed in 21 C.F.R. § 320.24 provide authority independent from § 320.22 for waiving the *in vivo* bioequivalence requirement found at 21 C.F.R. § 320.21.

4. FDA's action in amending its regulations without engaging in notice-and-comment rulemaking is contrary to the requirements of 5 U.S.C. § 553 of the Administrative Procedure Act ("APA") and is therefore invalid.

JURISDICTION AND VENUE

5. This Court has subject-matter jurisdiction over this action pursuant to 28 U.S.C. § 1331 (federal question); 5 U.S.C. §§ 701-06 (APA); and the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

6. Venue is proper in this district under 28 U.S.C. § 1391(e).

PARTIES

7. ViroPharma Incorporated ("ViroPharma") is a small pharmaceutical company that was incorporated in Delaware in 1994. ViroPharma is headquartered in Exton, Pennsylvania, and has approximately 200 employees.

8. ViroPharma is committed to the development and commercialization of products that address serious diseases, with a focus on products used by physician specialists or in hospital settings.

9. Defendant Department of Health and Human Services is an Executive department administered by Kathleen Sebelius, with responsibility under the Federal Food, Drug and Cosmetic Act ("FFDCA") for regulating drugs marketed in the United States. 21 U.S.C. §§ 301 *et seq.* HHS has its principal office at 200 Independence Ave., S.W., Washington, D.C. 20201.

10. Secretary Kathleen Sebelius executes the FFDCA through a delegation of authority to the Food and Drug Administration. 21 U.S.C. § 393(d)(2).

11. Defendant Food and Drug Administration is an operating division of HHS, and has its principal office at 5600 Fishers Lane, Rockville, Maryland 20857. FDA is responsible for regulating drugs marketed in the United States. 21 U.S.C. § 393.

12. Defendant Margaret A. Hamburg, M.D., is the Commissioner of Food and Drugs, with responsibility for executing the FFDCA, 21 U.S.C. § 393(d)(1), and has delegated authority to grant or deny citizen petitions to the Director of FDA's Center for Drug Evaluation and Research ("CDER"). *See* FDA Staff Manual Guides ("SMG") 1410.30, Petitions Under Title 21, Code of Federal Regulations (21 C.F.R.), Part 10.

STATEMENT OF FACTS

Vancocin®: Drug of Last Resort

13. In late 2004, ViroPharma acquired the exclusive right to market the prescription drug Vancocin® in the United States from Eli Lilly and Company.

14. Vancocin is the trade name for the FDA-approved drug vancomycin hydrochloride capsules.

15. Vancocin is taken orally in capsule form, and is used primarily to treat life-threatening gastrointestinal ("GI") infections caused by the bacteria *Clostridium Difficile* ("*C. difficile*") and *Staphylococcus aureus* ("*S. aureus*"). Vancocin is the only drug approved by FDA to treat *C. difficile* infections ("CDI").

16. Both types of infections, particularly CDI, are serious and can be life threatening.

17. Vancocin is not intended to be absorbed into the bloodstream but instead acts locally against these infections in the GI tract.

18. When CDI is severe enough to persist even after treatment with other drugs, Vancocin is viewed as the drug of last resort against this potentially fatal infection.

19. In recent years, the occurrence of CDI has increased dramatically, and an epidemic new strain has appeared that can trigger fulminant—that is, sudden and severe—disease within a few days.

20. Vancocin is one of only two drugs that ViroPharma markets, and is the primary source of ViroPharma's revenue.

21. Prior to acquiring Vancocin in 2004, ViroPharma had no sales revenue and sustained annual operating losses.

22. An important factor in ViroPharma's decision to acquire Vancocin in 2004 was FDA's pathway to generic competition for Vancocin. In order for generic drugs to be approved by FDA, they must be shown to be (among other requirements) bioequivalent to the innovator product. For orally administered drugs that produce their effects by local action in the GI tract, like Vancocin, bioequivalence must be demonstrated either through a study with clinical efficacy and safety endpoints, and/or an *in vitro* study that has been validated to correlate with important *in vivo* effects (which correlation can only be shown by clinical data).

23. Documents obtained from FDA by ViroPharma through litigation under the Freedom of Information Act ("FOIA") show that in 2005 and 2006, FDA privately communicated to several third parties that it had changed its bioequivalence requirements for generic copies of Vancocin and would accept data generated by *in vitro* methods that had not been correlated with *in vivo* effects. One such communication was sent to a Canadian stock analyst, which, on March 16, 2006, issued a report stating that its "recent communications with the FDA regarding the approval process for a potential generic competitor to Vancocin [led it] to believe a generic could enter the market 1-2 years sooner than current expectations."

24. The stock analyst's report was the first public disclosure of FDA's new bioequivalence standard for vancomycin and was the first ViroPharma itself learned of the new standard. At the time, Vancocin was the only drug marketed by ViroPharma, and the release of the stock analyst's report triggered a multi-day stock sell-off that cut ViroPharma's market capitalization by 40% (approximately $500,000,000).

25. As a result of the Canadian stock analyst's March 2006 announcement of FDA's willingness to accept uncorrelated *in vitro* data to establish bioequivalence for Vancocin, ViroPharma has ever since labored under a cloud of uncertainty that has materially and adversely

affected its entire business. ViroPharma has been forced to reject a number of clinical development initiatives that were under consideration to evaluate Vancocin in different clinical settings and patient populations. Further, ViroPharma has been forced to eliminate medical education efforts and promotional efforts for Vancocin. ViroPharma's business decisions have been and continue to be adversely affected by the uncertainty FDA's action creates regarding future Vancocin revenues.

26. ViroPharma relies on the revenue from Vancocin sales to fund its research and development of new drugs. The significant loss of market capitalization also has dramatically impacted ViroPharma's ability to fund the acquisition of additional products and product candidates. To this day, the impact of FDA's changed bioequivalence standard for Vancocin prevents many investors from investing in ViroPharma.

27. No ANDAs for generic versions of Vancocin have yet been approved. However, Vancocin is no longer subject to patent protection, and, upon information and belief, the absence of patent protection, the recent increase in infections related to *C. difficile*, which Vancocin is successful in treating, and FDA's change to an easier bioequivalence method for generic copies of Vancocin have led to increased interest in developing a generic version of Vancocin.

28. Documents obtained from FDA by ViroPharma through the FOIA litigation indicate that there are currently at least 11 ANDAs for vancomycin awaiting FDA approval.

Testing for Generic Bioequivalence

29. A drug manufacturer may file an ANDA with the FDA seeking approval to market a generic copy of an FDA-approved innovator drug. 21 U.S.C. § 355(j).

30. In light of FDA's findings of safety and effectiveness of the innovator drug, ANDAs can be approved without the generic manufacturer having to conduct costly clinical trials to demonstrate safety and efficacy.

31. To rely on an innovator drug's proven record of safety and effectiveness, the applicant must demonstrate that its drug product is bioequivalent to the brand drug referenced in its ANDA (known as the "Reference Listed Drug" or "RLD"). *See* 21 U.S.C. § 355(j)(4)(F).

32. In order for bioequivalence to be demonstrated, an ANDA filer must show that its drug, when compared to the RLD, has no significant difference in the rate and extent to which it becomes available at the site(s) of action. 21 U.S.C. § 355(j)(8).

33. For drugs intended to be absorbed into the bloodstream to reach the site of action (known as "systemically absorbed drugs"), bioequivalence is usually demonstrated by showing comparable profiles of an active ingredient's absorption into the bloodstream through blood tests, known as "pharmacokinetic" or "PK" studies, that measure the concentration of the active ingredient in the blood at various time intervals after administration. 21 U.S.C. § 355(j)(8)(B).

34. For drugs that are not intended to be absorbed into the bloodstream ("non-systemically absorbed" or "locally acting" drugs), such as Vancocin, the FFDCA gives FDA the authority to establish "alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect." 21 U.S.C. § 355(j)(8)(C).

35. Except in certain very limited circumstances, FDA's regulations require bioequivalence to be demonstrated through *in vivo* testing, *i.e.*, testing on humans. 21 C.F.R. § 320.21. *In vivo* testing methods can include analyses of blood levels through PK studies, analyses of a "pharmacodynamic" effect produced by the drug's activity at the local site of

action, and clinical endpoint bioequivalence studies that assess the equivalence of treatment with the generic product to treatment with the RLD in terms of safety and therapeutic effect.

Waiver of The *In Vivo* Testing Requirement

36. FDA regulations permit the *in vivo* bioequivalence testing requirement to be waived under certain limited circumstances. 21 C.F.R. §§ 320.21(f), 320.22.

37. FDA's regulations provide that an ANDA applicant seeking a waiver of the *in vivo* bioequivalence testing requirement "*shall* meet the criteria set forth in §320.22." 21 C.F.R. § 320.21(f) (emphasis added). Thus, under FDA regulations, the agency can only waive the *in vivo* bioequivalence testing requirement if the drug product meets one of the waiver criteria set forth in 21 C.F.R. § 320.22.

38. FDA's regulations also contain a section entitled "Types of evidence to measure bioavailability or establish bioequivalence," which discusses both *in vivo* and *in vitro* methods of establishing bioequivalence. 21 C.F.R. § 320.24.

39. 21 C.F.R. § 320.24 does not authorize the waiver of the *in vivo* bioequivalence requirement, which is the function of §§ 320.21 and 320.22. Rather, § 320.24 lists the various methods for establishing either *in vivo* or *in vitro* bioequivalence, depending on which of those two types of testing is otherwise required by the regulations.

40. In promulgating 21 C.F.R. § 320.24, FDA stated that it was intended simply "to state the methods that may be used *to meet* an in vivo or in vitro testing requirement." 54 Fed. Reg. 28,872, 28,912 (July 10, 1989) (emphasis added).

41. When originally promulgated, 21 C.F.R. § 320.21 had erroneously stated that in order to obtain a waiver, the ANDA applicant "shall meet the criteria set forth in § 320.24." *See* 57 Fed. Reg. 17,950, 17,998 (April 28, 1992). In 1998, FDA proposed a change to its regulations to correct this typographical error so that § 320.21 would correctly refer to § 320.22

and not to § 320.24. *See* 63 Fed. Reg. 64,222 (Nov. 19, 1998). This correction was made final in 2002. *See* 67 Fed. Reg. 77,668 (Dec. 19, 2002).

42. 21 C.F.R. § 320.22(a) states, in relevant part, that "FDA shall waive the requirement for the submission of evidence of *in vivo* bioavailability or bioequivalence if the drug product meets any of the provisions of (b), (c), (d), or (e) of this section." *Id.*

43. 21 C.F.R. § 320.22(b) allows the *in vivo* bioequivalence testing requirement to be waived for certain injectable, topical or oral solution, and inhalation drug products for which bioequivalence may be considered self-evident.

44. 21 C.F.R. § 320.22(c) provides for waiver of the *in vivo* bioequivalence testing requirement for DESI drugs. "DESI" drugs were approved solely on the basis of their safety prior to 1962. Congress later required that these drugs also be evaluated for their efficacy, leading FDA to initiate a program known as Drug Efficacy Study Implementation ("DESI") to evaluate the drugs' effectiveness.

45. 21 C.F.R. § 320.22(d)(2) provides for waiver of *in vivo* bioequivalence testing for a different strength of a drug product when bioequivalence has already been demonstrated through *in vivo* testing for at least one other strength of the drug product.

46. 21 C.F.R. § 320.22(d)(3) provides for waiver of *in vivo* bioequivalence testing where the drug product meets an *in vitro* bioequivalence testing method that has been correlated with *in vivo* data.

47. 21 C.F.R. § 320.22(d)(4) provides for waiver of *in vivo* bioequivalence testing for reformulated versions of previously-approved drug products where the reformulation only changes a color, flavor, or preservative that could not affect bioavailability.

48. 21 C.F.R. § 320.22(e) provides for waiver of *in vivo* bioequivalence for good cause, if waiver is compatible with the protection of public health. FDA inserted the "good cause" regulation *sua sponte* in its 1977 final bioequivalence rule for the limited situations where it was "necessary to allow FDA to permit the continued marketing of medically important drug products while adequate methodology is being developed or bioavailability studies are being conducted." Bioavailability and Bioequivalence Requirements, Final Rule, 42 Fed. Reg. 1638, 1642 (Jan. 7, 1977). Thus, the waiver applies only where necessary for the continued marketing of a drug, not for drugs, like Vancocin, that continue to be marketed.

FDA Amends Its Regulations for Waiver of The *In Vivo* Testing Requirement

49. On November 9, 2007, Cobalt submitted a Citizen Petition and request for a stay of action claiming that ANDA applicants for the locally acting GI drug Precose (acarbose) could not qualify for a waiver of the *in vivo* bioequivalence requirement under 21 C.F.R. §§ 320.21 and 320.22. *See* Cobalt Citizen Petition regarding Precose® (acarbose), Docket No. FDA-2007-P-0418 (formerly Docket No. 2007P-0448) (Nov. 9, 2007) (the "Acarbose Bioequivalence Petition") (attached hereto as Ex. 1).

50. FDA denied Cobalt's request for a stay of action and justified its authority to approve acarbose ANDAs based solely on *in vitro* testing even in the absence of any of the waiver criteria of § 320.22. *See* FDA Citizen Petition Response regarding Precose® (acarbose), Docket No. FDA-2007-P-0418 (May 7, 2008) (the "Acarbose Bioequivalence Decision") (attached hereto as Ex. 2).

51. FDA claimed that under "§ 320.24 of its regulations, FDA has the discretion to accept in vitro studies for a nonsystemically absorbed drug product such as acarbose when such studies are determined to be a scientifically valid method of determining bioequivalence." Acarbose Bioequivalence Decision at 6.

52. Through this response, FDA effectively amended its regulations, which on their face plainly require that one of the waiver criteria of § 320.22 be satisfied before FDA can waive the *in vivo* requirement. Instead, FDA interpreted the list of bioequivalence methods provided in 21 C.F.R. § 320.24 as a separate and sufficient regulatory basis for waiving *in vivo* bioequivalence requirements independent of 21 C.F.R. § 320.22.

53. FDA's denial of Cobalt's Acarbose Bioequivalence Petition completed the Citizen Petition process and was final agency action.

54. Before issuing its Acarbose Bioequivalence Decision, FDA did not publish a notice in the Federal Register—or anywhere else—indicating that it was considering amending its regulations for *in vivo* bioequivalence requirements by removing the requirement that one of the waiver criteria in § 320.22 be satisfied in order for ANDAs to be approved based solely on *in vitro* testing, nor did it provide for public notice and comment prior to issuing its amended regulation.

55. Thus, ViroPharma was denied the opportunity to participate in notice-and-comment rulemaking before FDA amended regulations that affect ViroPharma's interests.

56. Moreover, the rule change potentially affects many drugs other than Vancocin. Thus, numerous other drug companies, as well as patients who use the affected drugs and the doctors who prescribe them, were also denied the opportunity to review and comment on the revised regulations.

57. As recently as June 2010, FDA has reiterated its position that § 320.24 provides an independent basis for waiving the *in vivo* bioequivalence testing requirement of § 320.21 even when none of the criteria of § 320.22 are satisfied.

58. In August 2007, prior to FDA's Acarbose Bioequivalence Decision, ViroPharma had commented on FDA's Draft Guidance for Industry entitled "Bioequivalence Recommendations for Specific Products" released in May 2007 (the "Draft Product Specific Bioequivalence Guidance"). In those comments, ViroPharma explained that, for orally administered locally-acting gastrointestinal drugs, FDA's regulations (§ 320.22(d)(3)) require the correlation of *in vitro* studies with *in vivo* effects. *See* Letter from T. Doyle to FDA (Aug. 29, 2007) Docket No. FDA-2007-D-0369-0004.1 at 4-5.

59. In 2006, ViroPharma also filed a petition for stay of action regarding the bioequivalence standards applicable to vancomycin. *See* ViroPharma's Petition for Stay of Action, Docket No. 2006P-0124 (later renamed Docket No. FDA-2006-P-0007 (March 17, 2006). In one of its amendments to that petition, ViroPharma explained that the rule announced in FDA's Acarbose Bioequivalence Decision was inconsistent with FDA's bioequivalence regulations. Specifically, ViroPharma explained that 21 C.F.R. § 320.21 requires that one of the specifically enumerated waiver criteria in § 320.22 be met before *in vitro* testing can be accepted to demonstrate bioequivalence. *See* ViroPharma Petition for Stay of Action Supplement, Docket No. 2006-P-007-18.1 (July 25, 2008) at 5-9.

60. ViroPharma further explained that FDA could only change its regulations through notice-and-comment rulemaking as required by the Administrative Procedure Act (5 U.S.C. § 553). *Id.* at 9.

61. In June 2010, after receiving ViroPharma's submissions, in both its amended petition for stay of action and its comments on the Draft Product Specific Bioequivalence Guidance, FDA released its Final Product Specific Bioequivalence Guidance. *See* CDER

Guidance for Industry "Bioequivalence Recommendations for Specific Products" (June 2010), Docket No. FDA-2007-D-0433.0005.

62. The Final Product Specific Bioequivalence Guidance included the following sentence that was not found in the Draft Product Specific Bioequivalence Guidance:

> For a drug that is not intended to be absorbed into the bloodstream, FDA may establish alternative methods to show bioequivalence that may be expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect (21 U.S.C. 355(j)(8)(C); **21 CFR 320.24**).

Id. at 2 (emphasis added).

63. In citing 21 C.F.R. § 320.24 in the Final Product Specific Bioequivalence Guidance as the sole regulatory basis for its decision to waive *in vivo* testing, FDA plainly ignored both the plain text of its own regulations and ViroPharma's submissions explaining that one of the criteria of § 320.22 must first be satisfied in order for FDA to waive the *in vivo* bioequivalence testing requirement of § 320.21, and affirmed the rationale it enunciated in its Acarbose Bioequivalence Decision.

64. By reaffirming its amendment to the regulations in the Final Product Specific Bioequivalence Guidance without first engaging in notice-and-comment rulemaking, FDA also ignored black letter law and ViroPharma's submission explaining that the APA requires such process before FDA can change its regulations.

Economic Impact of FDA's Amendment on ViroPharma

65. Because no ANDAs for vancomycin hydrochloride capsules have been approved, ViroPharma currently enjoys strong demand for Vancocin in the United States.

66. FDA's amended regulations greatly increase the likelihood of approvals for generic vancomycin ANDAs.

67. Before FDA amended its regulations, ANDA applicants were required to establish bioequivalence by using the more rigorous and costly *in vivo* methods or prove that one of the specifically enumerated waiver provisions of 21 C.F.R. § 320.22 was satisfied in order to receive approval based solely on *in vitro* testing methods.

68. None of the waiver criteria of 21 C.F.R. § 320.22 applies to vancomycin capsules: vancomycin capsules are not an injectable, topical or oral solution, or inhalation drug product (§ 320.22(b)); vancomycin is not a DESI drug (§ 320.22(c)); vancomycin capsule ANDAs do not seek approval of a different strength of a drug product that has already been approved (§ 320.22(d)(2)); *in vitro* bioequivalence methods for vancomycin have not, to ViroPharma's knowledge, been shown to be correlated with *in vivo* data (§ 320.22(d)(3)); vancomycin capsule ANDAs do not seek approval for a reformulation of an already-approved product (§ 320.22(d)(4)); nor is there a need to approve vancomycin capsule ANDAs to ensure the continued marketing of a medically important drug product because Vancocin is readily available in the market (§ 320.22(e)).

69. Because vancomycin does not satisfy any of the criteria of § 320.22, until FDA changed its regulations, sponsors of vancomycin capsule ANDAs had to perform the more rigorous and costly *in vivo* bioequivalence testing in human subjects.

70. Because FDA's amended regulations now allow ANDA applicants to bypass the requirements of § 320.22 and establish bioequivalence based solely on *in vitro* methods that have not been correlated with *in vivo* data, establishing bioequivalence to Vancocin is now easier and less costly, making it more likely that vancomycin capsule ANDAs will obtain FDA approval.

71. The increased likelihood of vancomycin capsule ANDA approvals continues to restrict ViroPharma's business decisions and impact its ability to raise capital and attract investors.

72. In addition, documents obtained from FDA by ViroPharma through litigation under the FOIA indicate that FDA has received at least 11 ANDAs for vancomycin capsules, and approval of generic versions of Vancocin appears imminent.

73. Indeed, at least one ANDA filer, Akorn, Inc., has progressed so far in the ANDA approval process as to have obtained final labeling approval from FDA.

74. Akorn's labeling was erroneously posted to the National Institute of Health ("NIH") website in July 2010. The NIH website provides a repository of labeling for all FDA-approved drugs, which it obtains from FDA's own electronic labeling-approval system.

75. The labeling that was posted on NIH's website contained a "Marketing Start Date" for Akorn's product of June 30, 2010. While the release of this labeling was premature, because Akorn's ANDA was not approved on June 30, 2010, and in fact has not yet been approved, the publication of the final labeling indicates that Akorn's ANDA is close to approval.

76. ViroPharma will be injured in the form of lost sales as a result of the approval of vancomycin ANDAs based on FDA's amended regulations.

77. Based on historical industry data, it is expected that sales of Vancocin will decrease by as much as 60% within the first three months of generic entry. Depending on the number and timing of generic approvals, the rate of the decrease of Vancocin sales could be much higher.

Count I- APA: Action Taken Without Observance of Procedure Required by Law

78. ViroPharma repeats, and incorporates by reference, paragraphs 1- 78 as if fully set forth herein.

79. FDA violated the Administrative Procedure Act by failing to engage in notice-and-comment rulemaking before effectively amending its regulations to permit waiver of the *in vivo* bioequivalence requirement based on 21 C.F.R. § 320.24 even when none of the waiver criteria of 21 C.F.R. § 320.22 are satisfied.

80. FDA's failure to engage in notice-and-comment rulemaking denied the interested public—including ViroPharma—the opportunity to evaluate the basis for, and meaningfully comment on, FDA's decision to effectively amend its bioequivalence regulations to broaden the situations in which *in vivo* waivers will be granted.

81. FDA thus adopted the new bioequivalence method "without observance of procedure required by law," and the new rule must be held unlawful and set aside. 5 U.S.C. § 706(2)(D).

Prayer for Relief

Wherefore, ViroPharma requests that the Court issue an Order:

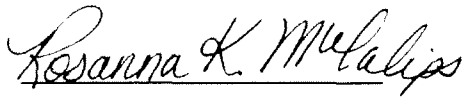
A. Declaring that the plain reading of FDA's regulations requires an ANDA applicant seeking a waiver of the *in vivo* bioequivalence testing requirement to first meet one of the criteria set forth in 21 C.F.R. § 320.22;

B. Declaring that FDA's statement in its Acarbose Bioequivalence Decision that 21 C.F.R. § 320.24 provides an independent basis for waiving the *in vivo* testing requirement even when none of the criteria of 21 C.F.R. § 320.22 is satisfied constitutes an amendment to FDA's regulations;

C. Declaring that FDA's amendment of its regulations governing waiver of submission of *in vivo* bioequivalence evidence, without engaging in notice-and-comment rulemaking, violates 5 U.S.C. § 553 of the APA and is therefore invalid; and

D. Ordering any other relief the Court may deem just and proper.

Respectfully submitted,



Dated: September 10, 2010

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Exhibit 1

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November 9, 2007

VIA MESSENGER

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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

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).[1] 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."

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[1] 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.

21 U.S.C. § 355(j)(8)(B).

(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.[2]

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.*).

[2] 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 ^{14}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.[3]

IV. Conclusion.

For the reasons cited above, Petitioner requests that FDA:

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[3] 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 petition 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

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.

Exhibit 2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

William A. Rakoczy
Rakoczy Molino Mazzochi Siwik, LLP
6 West Hubbard Street
Suite 500
Chicago, IL 60610

MAY 7 2008

Re: Docket No. FDA-2007-P-0418

Dear Mr. Rakoczy:

This letter responds to your citizen petition (Petition) and petition for stay of action (PSA), dated November 9, 2007, submitted on behalf of Cobalt Laboratories Inc. and Cobalt Pharmaceuticals Inc. (Cobalt).[1] The Petition asks the Food and Drug Administration (FDA or Agency) to (1) require all applicants submitting an abbreviated new drug application (ANDA) referencing Bayer's new drug application (NDA) 20-482 for Precose (acarbose) to conduct in vivo bioequivalence tests and studies comparing the proposed generic product to Precose, the reference listed drug (RLD); (2) refrain from granting any in vivo bioequivalence waiver for any ANDA referencing Bayer's NDA 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 CFR 320.21. The PSA requests that FDA stay approval of any ANDA for acarbose tablets, unless and until such ANDA contains sufficient evidence and data from in vivo bioequivalence testing. As explained in this response, your Petition is granted in part and denied in part, and your PSA is denied.[2]

I. Background

A. Precose

Precose (acarbose) tablets (NDA 20-482) were initially approved on September 6, 1995. Precose is approved as monotherapy as an adjunct to diet to lower blood glucose in patients with type 2 diabetes mellitus whose hyperglycemia cannot be managed on diet alone. Precose may also be used in combination with a sulfonylurea when diet plus either Precose or a sulfonylurea do not result in adequate glycemic control. Also, Precose may be used in combination with insulin or metformin.

The active ingredient in Precose is acarbose, an oligosaccharide isolated from cultures of the gram-positive actinobacteria. Acarbose reversibly inhibits α-glucosidases, which are

[1] This Petition and PSA were originally assigned docket number 2007P-0448/CP1 & PSA1. The number was changed to FDA-2007-P-0418 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] Today we are approving two ANDAs for generic versions of acarbose, including Cobalt's ANDA.

enzymes responsible for the breakup of starch into simpler sugar molecules. Glucosidases are present in the brush-border on the small intestinal mucosa. Acarbose delays the digestion of ingested carbohydrates, thereby resulting in a smaller rise in blood glucose concentration following meals. As a consequence of plasma glucose reduction, acarbose reduces levels of glycosylated hemoglobin in patients with type 2 diabetes mellitus. In healthy subjects, acarbose is shown to be poorly absorbed, with systemic bioavailability of less than 2 percent (0.5 to 1.7%). Acarbose is metabolized exclusively within the gastrointestinal (GI) tract by intestinal bacteria and digestive enzymes. According to the labeling for Precose, less than 2 percent of the oral dose was recovered in urine, consistent with low bioavailability of the drug. Because acarbose acts locally within the GI tract, this low systemic availability is therapeutically desired.

B. Summary of Statutory and Regulatory Basis for ANDA Approval

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)), which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the RLD[3] is safe and effective. Under the Hatch-Waxman Amendments, to rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its generic drug[4] is bioequivalent to the RLD.[5] In addition, a drug product described in an ANDA generally must contain the same active ingredient,[6] conditions of use,[7] route of administration, dosage form, strength,[8] and (with certain permissible differences) labeling[9] as the RLD, unless a petition for certain changes is approved by the Secretary[10] (section 505(j)(2)(A),

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[3] A reference listed drug or RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, which is generally known as the *Orange Book*.

[4] For purposes of this response, the term *generic drug* refers to new drug products for which approval is sought in an ANDA submitted under section 505(j) of the Act.

[5] See, e.g., section 505(j)(2)(A)(iv) of the Act (requiring "information to show that the new drug is bioequivalent to the listed drug referred to in clause (i) [i.e., listed drug]..."); 21 CFR 314.3 (defining *reference listed drug*); 21 CFR 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the reference listed drug upon which the applicant relies); 21 CFR 314.127(a)(6)(i)(providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA); and the Orange Book, Introduction at x (defining *reference listed drug*).

[6] See, e.g., 21 CFR 314.94(a)(5).

[7] See, e.g., 21 CFR 314.94(a)(4).

[8] See, e.g., 21 CFR 314.94(a)(6).

[9] See, e.g., 21 CFR 314.94(a)(8).

[10] An applicant may submit an ANDA for a drug that has a different active ingredient, route of administration, dosage form, or strength from the RLD if the applicant has submitted a petition to the

(j)(2)(C), and (j)(4) of the Act). Drug products that meet the approval requirements under section 505(j) and are both bioequivalent and pharmaceutically equivalent[11] to the RLD are considered by FDA to be therapeutically equivalent to the RLD. Therapeutically equivalent drugs generally may be substituted for each other with the expectation that the substituted product will produce the same clinical effect and safety profile when used according to the labeling.[12]

The statute, regulations, and case law give FDA and ANDA applicants considerable flexibility in determining how this requirement for establishing bioequivalence can be met. Section 505(j)(8)(B)(i) of the Act states that a generic drug is bioequivalent to the RLD if the following conditions exist:

> . . . 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 . . .[13]

However, section 505(j)(8)(C) of the Act recognizes that different approaches may apply to locally acting, nonsystemically absorbed drug products. It states the following:

> For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

FDA's regulations similarly reflect the flexibility that FDA has in choosing the appropriate methods to establish bioequivalence for particular drug products. In 21 CFR 320.1(e), FDA defines bioequivalence (in part) as follows:

> . . . the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of

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Agency (known as a *suitability petition*) requesting permission to file such an application and has received the Agency's approval (see section 505(j)(2)(C) of the Act and 21 CFR 314.93).

[11] Pharmaceutically equivalent drug products have the same dosage form and contain the same amounts of the same active drug ingredient and meet the same compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. They do not necessarily contain the same inactive ingredients and may also differ in characteristics such as shape, scoring, release mechanism, and, within certain limits, labeling (see 21 CFR 320.1 and the Orange Book, Introduction at p. vii).

[12] See the Orange Book, Introduction at p. vii.

[13] See also 21 CFR 320.1(e) and 320.23(b).

> drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Although an ANDA applicant is required to submit "[e]vidence demonstrating that the drug product that is the subject of the [ANDA] is bioequivalent to the reference listed drug[,]"[14] the regulations explicitly permit submission of "information to show that the drug product is bioequivalent to the reference listed drug which would permit FDA to waive the submission of evidence demonstrating in vivo bioequivalence. . . "[15]

The regulations similarly make clear that although in vivo studies may be the preferred method to demonstrate bioequivalence in many cases, it is not the only permissible method. On the contrary, under the regulations, "bioequivalence may be demonstrated by several in vivo and in vitro methods." The regulations provide the following:

> FDA may require in vivo ***or in vitro testing, or both***, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products [emphasis added]. . . . The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.[16]

FDA regulations at 21 CFR 320.24 describe these methods in descending order of accuracy, sensitivity, and reproducibility. They include (1) in vivo pharmacodynamic effect studies, (2) clinical trials, (3) in vivo animal studies, and (4) in vitro studies.[17] In addition, as under section 505(j)(8)(C) of the Act, § 320.24(b)(6) of the regulations states that FDA has the flexibility to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence." Similarly, the waiver provisions of the regulations provide that waivers of in vivo bioequivalence may be given in many specific situations and, even if none of those situations are present, in vivo bioequivalence may be waived "for good cause . . . if waiver is compatible with the protection of the public health."[18]

Ultimately, under the statute and regulations, the choice of study design is based on the ability of the design to compare the drug delivered by the two products at the particular site of action of the drug. The courts that have considered FDA's bioequivalence methodologies have also consistently upheld FDA's scientific discretion in this regard

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[14] 21 CFR 320.21(b)(1).

[15] 21 CFR 320.21(b)(2).

[16] 21 CFR 320.24(a).

[17] 21 CFR 320.24.

[18] 21 CFR 320.22(e).

(see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390 at 397-400 (3rd Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994); *Bristol Myers Squibb Co. v. Shalala*, 923 F. Supp. 212 (D.D.C. 1996)). As the *Bristol Myers Squibb* court noted, FDA has been given "the discretion to determine whether in vitro, or in vivo bioequivalence studies, or both, are required for the approval of generic drugs under the abbreviated application process" (*id.* at 217). Thus, bioequivalence for different types of drug products can be shown in different ways.

For absorbed and systemically acting drug products, the rate and extent of systemic absorption is usually the most sensitive, accurate, and reliable indicator of the rate and extent to which the active ingredient becomes available at the site of drug action. The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption, therefore, usually rests on a pharmacokinetic comparison of drug and/or metabolite concentrations in an accessible biologic fluid, such as blood, after administration of a single dose of each drug product to healthy volunteers.

For locally acting, nonsystemically absorbed or low bioavailability oral drug products, such as acarbose, however, a traditional in vivo bioequivalence study comparing rate and extent of absorption of the active ingredient into the bloodstream would be of limited utility. Instead, other designs would be preferable to determine the rate at which a locally acting, nonsystemically absorbed drug product becomes available at the site of drug action. For such drugs, a showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of action at a rate and extent that is not significantly different from that of the RLD, along with satisfaction of the other requirements for ANDA approval, may permit FDA to conclude that the proposed generic drug can be expected to behave the same way in the body as the RLD.

II. Discussion

You request that FDA require all applicants submitting an ANDA referencing Bayer's NDA 20-482 for Precose (acarbose) to conduct in vivo bioequivalence tests and studies comparing the proposed generic product to Precose and to refrain from granting any such ANDA an in vivo bioequivalence waiver. You also ask the Agency to 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 section 505(j)(8)(A)(ii) and § 320.21.

A. Permissibility of In Vitro Bioequivalence Testing

In making your case for FDA to require in vivo bioequivalence tests for all ANDA applicants referencing Precose and to refrain from granting any biowaivers, you suggest that there are only two potential bases to grant a waiver for acarbose and assert that both would be inappropriate for FDA to use in this case. The first theory is that FDA is waiving in vivo bioequivalence under 21 CFR 320.22(c). This regulation permits a waiver of in vivo bioequivalence testing for (1) certain drug products that were determined to be effective in a Drug Efficacy Study Implementation (DESI) notice or (2)

a drug product that is identical, related, or similar to such a DESI drug. You argue that acarbose was never the subject of a DESI notice and is not identical, related, or similar to a DESI drug (Petition at 3-4).

Your second theory is that FDA is waiving in vivo bioequivalence under the Biopharmaceutics Classification System (BCS). FDA's guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (BCS Guidance)[19] provides recommendations for requesting a waiver of in vivo bioavailability and bioequivalence studies for systemically acting solid oral dosage forms. In the case of ANDAs, the BCS Guidance recommends that applicants obtain biowaivers for Class 1 substances (i.e., rapidly dissolving, immediate-release test products containing highly soluble and highly permeable drug substances), provided that the reference listed drug product is also rapidly dissolving and the test product exhibits similar dissolution profiles to the reference listed drug product. You theorize that we consider acarbose to be a Class 1 drug substance, and we would grant a biowaiver on this basis. You then assert that acarbose does not meet the qualifications for a BCS biowaiver because it is a Class 3 substance (high solubility and low permeability) under the BCS Guidance (Petition at 8-9).

We have not relied on either of your two asserted theories, yet we have nonetheless concluded that in vitro studies are appropriate to establish bioequivalence for acarbose under certain circumstances. Acarbose was not a DESI product (or a similar or related product) and we do not consider it to be a Class 1 drug substance. Rather, we consider it to be a Class 3 drug substance. However, the BCS Guidance does not address the bioequivalence criteria for drugs that do not act systemically (i.e., do not act following absorption into the bloodstream).[20] Therefore, its status as a Class 3 drug substance is not dispositive. You claim that FDA has no discretion to waive in vivo bioequivalence for any reason other than your two asserted theories. We disagree. Under section 355(j)(8)(C) of the Act and § 320.24 of the regulations, FDA has the discretion to accept in vitro studies for a nonsystemically absorbed drug product such as acarbose when such studies are determined to be a scientifically valid method of determining bioequivalence (see, e.g., *Bristol-Myers Squibb Co.*, 923 F. Supp. 212 (D.D.C. 1996)).[21]

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[19] Available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

[20] For a systemically acting drug, high solubility and high permeability results in the drug's complete absorption and high bioavailability at the site of action. Thus for systemically acting drugs, the BCS Guidance identifies highly soluble, highly permeable drugs as Class 1 and appropriate for biowaiver. However, for drugs that act locally in the GI tract, such as acarbose, it is the poor permeability that generally assures no loss of bioavailability due to absorption. For this reason, these drugs may be appropriate for in vitro testing under certain circumstances, even though they are not Class 1 drugs as described in the BCS Guidance.

[21] Even if a waiver of in vivo bioequivalence is required before we can accept in vitro studies, as described in section II.B of this response, for certain acarbose drug products such a waiver is compatible with the public health under 21 CFR 320.22(e) and therefore permissible and appropriate.

After receiving your Petition and considering all of the submissions in the petition docket, FDA carefully examined all of our recommendations for demonstrating bioequivalence for a generic acarbose and Precose. Although you established bioequivalence for your generic acarbose tablets using in vivo bioequivalence testing, we do not believe that such in vivo testing is required. Given that the drug product acts locally in the GI tract and is not systemically absorbed, we believe that the appropriate criteria for establishing bioequivalence for acarbose may be in vitro testing or in vivo testing with a pharmacodynamic endpoint, depending on the similarity of the formulations of the test and reference products. In the case of a generic acarbose with active and inactive ingredients that are qualitatively and quantitatively the same as Precose, we recommend in vitro, rather than in vivo, testing for establishing bioequivalence.

B. Appropriate Circumstances for In Vivo or In Vitro Bioequivalence Testing

We find that in vitro testing is an appropriate means of demonstrating bioequivalence between a generic acarbose and Precose under certain circumstances. Specifically, for evaluating the bioequivalence of generic acarbose oral tablets, FDA recommends either in vitro or in vivo studies, depending on the similarity of the formulations of the test and reference products. If the test product formulation is qualitatively (Q_1) (i.e., contains all of the same active and inactive ingredients) and quantitatively (Q_2) the same as the RLD with respect to active and inactive ingredients, the bioequivalence of all tablet strengths can be established based solely on comparative dissolution (in vitro study). If the test product formulations are not qualitatively (Q_1) and quantitatively (Q_2) the same as Precose with respect to inactive ingredients, bioequivalence needs to be established by conducting a study with pharmacodynamic endpoints (in vivo study).[22]

A comparison of in vitro dissolution profiles in multiple media, along with a regulatory determination of formulation similarity (i.e., Q_1/Q_2), is an appropriate method for evaluating the bioequivalence of generic acarbose oral tablets based on the following factors:

- Acarbose is poorly absorbed with systemic bioavailability of less than 2 percent, and it acts locally in the GI tract. This low permeability assures minimal loss of bioavailability due to absorption.
- The rate and extent of drug release to the site of action is affected by the in vivo dissolution of the acarbose tablets, in addition to gastric emptying and GI motility.
- High solubility and relatively fast dissolution ensure that this product forms a solution and stays in solution, before it reaches the site of action (small intestine). Therefore, once dissolved, local distribution of acarbose in the GI tract should be similar for a test (generic) product and the RLD.

[22] A generic acarbose will be considered Q_1/Q_2 if (1) the amount of any excipient is no more than ± 5% different from the corresponding excipient in Precose, and (2) the total weight of the test product tablet is no more than ± 5% different from the total weight of the Precose tablet.

If the two products are Q_1/Q_2, then the only possible difference that would affect the bioavailability at the site of action in the GI tract is the rate of dissolution, a property that can be measured accurately in vitro. Once dissolved, the local distribution of acarbose in the GI tract should be similar for a test (generic) product and Precose.

In cases where a generic acarbose is not Q_1/Q_2, it is possible that different excipients or different amounts of an excipient may interact with the mechanism of the drug to inhibit glucosidases. Dissolution testing would not be adequate to ensure that there is no unique interaction between an excipient and the mechanism of action of the active ingredient. Therefore, in those circumstances, we recommend an in vivo bioequivalence study. The in vivo study would use a pharmacodynamic endpoint to determine whether differences in the type or amounts of excipients between the generic product and Precose affect bioavailability.[23] The most appropriate endpoint for such a study would be change in blood glucose concentrations because acarbose works by delaying digestion of ingested carbohydrates, thereby resulting in a smaller rise in blood glucose concentration following meals.

In cases where an in vivo study is needed, FDA recommends a pilot study first be conducted to determine the appropriate dose for the pivotal bioequivalence study and to determine the appropriate number of study subjects needed to provide adequate statistical power to establish bioequivalence in the pivotal study. The pilot study should use the RLD (Precose tablets) given with 75 grams of sucrose, and should identify the lowest possible dose that will yield a pharmacodynamic response statistically significantly different from the control at alpha=0.05 (two-sided), equivalent to alpha=0.025 (one-sided). This approach ensures that a significant glucose-lowering pharmacodynamic response is obtained that is not near the plateau of the dose-response curve. A response near the plateau would exhibit decreased sensitivity to delivered dose differences between products. The first dose tested is recommended to be a Precose 25-milligram (mg) tablet. If treatment with this dose does not elicit a measurable response relative to the control, it may be necessary to repeat the study with multiples of the 25-mg strength, beginning with two 25-mg tablets. The treatments to establish the appropriate dose can be studied in the same group of subjects, with a 1-week washout between each treatment, until the optimal dose for the pivotal study is identified.

III. Request for Stay

In the PSA, you request that FDA stay approval of any ANDA for acarbose tablets unless and until such ANDA contains sufficient evidence and data from in vivo testing to establish bioequivalence in accordance with 21 U.S.C. 355(j), 21 CFR 320.21, and 21 CFR 320.23 (PSA at 1). You reiterate the position in your Petition that FDA may not waive the requirement for the submission of evidence demonstrating in vivo

[23] Because acarbose is not intended to be systemically absorbed and has very low bioavailability following oral administration, a traditional pharmacokinetic study that measures blood levels of the active ingredient over time would be of limited value in comparing the formulations of two acarbose oral products.

bioequivalence (PSA at 2). You state that Cobalt faces irreparable injury in the absence of a stay and that your request is not frivolous and is being pursued in good faith (PSA at 3).

FDA's regulation at 21 CFR 10.35(e) sets out the standard for review of a petition for stay of action as follows:

> The Commissioner may grant or deny a petition, in whole or in part; and may grant such other relief or take such other action as is warranted by the petition. The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice. The Commissioner shall grant a stay in any proceeding if all of the following apply:
>
> (1) The petitioner will otherwise suffer irreparable injury.
> (2) The petitioner's case is not frivolous and is being pursued in good faith.
> (3) The petitioner has demonstrated sound public policy grounds supporting the stay.
> (4) The delay resulting from the stay is not outweighed by public health or other public interests.

As stated in the regulation, the Commissioner shall grant a stay if all four of these criteria apply.

We need not address your irreparable harm argument[24] or whether your request is not frivolous and is being pursued in good faith because we have determined that you have failed to (1) demonstrate public policy grounds for the stay and (2) show that the delay would not be outweighed by public health or other public interests.

A. Sound Public Policy Grounds Do Not Support the Stay

You have not demonstrated that sound public policy grounds exist in support of the stay. You maintain that granting the stay will ensure that FDA follows the required approval criteria for ANDAs. You also assert that without in vivo bioequivalence testing of a generic acarbose product, there may be safety concerns (PSA at 3).

Your argument assumes that FDA has not complied with the requirements of the statute or regulations for approval of a generic acarbose. We disagree. As explained in section I.B of this response, FDA has flexibility to establish appropriate tests for the demonstration of bioequivalence. In the case of acarbose, as explained in section II.B, it is appropriate to permit in vitro dissolution testing for certain generic acarbose ANDAs (if they also demonstrate that the product is Q_1/Q_2 to Precose). For all other generic

[24] We note, however, that you have not demonstrated that you would suffer irreparable harm. Indeed, you do not describe any harm that you would suffer as a result of denying your PSA. You merely assert that it would be unlawful for FDA to waive in vivo bioequivalence requirements for acarbose and that we cannot force Cobalt to compete with applicants that have not conducted in vivo bioequivalence testing.

acarbose products, in vivo testing is appropriate. You have not described any specific safety concerns that may be associated with FDA's approach to bioequivalence testing. In addition, you have not described any safety issues that may result from our acceptance of in vitro bioequivalence testing in the limited circumstances described above. We note that although Cobalt sought FDA's advice on the appropriate bioequivalence testing for generic acarbose, you did not wait for a response before you began your in vivo bioequivalence testing. You were under no obligation to await FDA's advice in this matter; however, had you done so, you would have been advised that in vivo bioequivalence testing was unnecessary for products that are Q_1/Q_2 to Precose.

B. Delay Would Be Outweighed by Public Health or Other Public Interests

You claim that the public's interest in appropriate application of the generic approval requirements outweighs its interest in immediate access to a competing generic product. You also claim that a temporary stay will not harm others because Cobalt is entitled to 180-day generic exclusivity (PSA at 3).

Based on the circumstances in this case, we conclude that the delay necessitated by the stay is outweighed by countervailing public health interests in approving acarbose ANDAs. As discussed previously in section III.A, your argument assumes that ANDA applicants are not complying with applicable statutory and regulatory requirements and the Agency's approval standards will be found inadequate. However, FDA expects ANDA applicants to meet applicable statutory and regulatory standards, as explained in detail in section II of this response. In addition, we note that Cobalt is not entitled to 180-day exclusivity.[25]

Moreover, delaying approval of ANDAs would frustrate the public policies underlying the Hatch-Waxman Amendments and the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85), among others.[26] One of the purposes of the Hatch-Waxman Amendments is to foster the availability of low-cost alternatives to previously approved drugs. This public policy goal would be frustrated if FDA were to grant this requested stay and treat pending ANDAs differently than other approved drug products.

IV. Conclusion

As discussed above, FDA's decision to permit the use of in vitro dissolution studies for establishing bioequivalence for generic acarbose oral tablets when the test and reference products are Q_1 and Q_2 is appropriate scientifically and in accordance with the Act and our regulations. Therefore, your request that all ANDA applicants conduct in vivo

[25] See response in Docket No. 2007-P-0249 issued today.

[26] Section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), 121 Stat. 953, adds new section 505(q) of the Act (21 U.S.C. 355(q)) and applies to certain citizen petitions and petitions for stay of action regarding the approval standards for generic drugs. Section 505(q)(1)(F) requires the Agency to respond to citizen petitions and petitions for stay of action such as yours no later than 180 days after submission.

bioequivalence testing is denied. Consistent with that decision, your request that in vivo bioequivalence waivers not be granted to ANDA applicants also is denied. However, because FDA has determined that in vivo bioequivalence testing is required if the test product is not Q_1 and Q_2 to the reference product, your request that ANDA applicants conduct in vivo bioequivalence testing is granted in part. In conclusion, the Petition is granted in part and denied in part. Your PSA is denied because you have failed to demonstrate that (1) sound public policy grounds support a stay and (2) delay is not outweighed by public health or other public interests.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research