Pfizer Inc
235 East 42nd Street 235/24/10A
New York, NY 10017-5755
Tel 212 733 5225 Fax 646 383 9498
Email Jeffrey.b.chasnow@pfizer.com

Jeffrey B. Chasnow
Assistant General Counsel
Legal Division

October 4, 2006

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

CITIZEN PETITION

Pfizer Inc. ("Pfizer") submits this petition under the Federal Food, Drug, and Cosmetic Act ("FFDCA") to request that the Food and Drug Administration ("FDA") take appropriate remedial action against the apparent misbranding of generic azithromycin for oral suspension marketed by Pliva, Inc. ("Pliva"). In addition, Pfizer urges FDA to reexamine the Pliva Abbreviated New Drug Application ("ANDA") filed for azithromycin for oral suspension, to ensure that it contains accurate and complete information regarding the active ingredient contained in the Pliva product.

Pfizer submitted similar petitions to FDA on February 9, 2006 (Docket No. 2006P-0070) and May 25, 2006 (Docket No. 2006P-0224), urging FDA to take action against Teva Pharmaceuticals USA, Sandoz Inc., and Pliva, respectively, on grounds that their generic azithromycin *tablet* products were misbranded. The current Citizen Petition addresses Pliva's generic azithromycin for oral suspension product.

A. Actions Requested

The generic azithromycin for oral suspension product marketed by Pliva appears to be misbranded because its label incorrectly identifies the polymorphic[1] form of

[1] FDA defines polymorphic form to refer to, *inter alia*, solvate and hydrate forms. FDA further describes solvates as "crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. If

the active ingredient[2] contained in the product. This discrepancy is significant because, as FDA consistently has noted, differences in polymorphic forms may affect drug quality, safety, and efficacy. In response to the misbranding of this product, Pfizer requests that FDA initiate a recall of the Pliva azithromycin for oral suspension product so that its labeling can be corrected.

In addition, Pfizer urges FDA to reexamine the ANDA for the azithromycin for oral suspension filed by Pliva to ensure that it contains complete and accurate information (including appropriate stability, dissolution, and bioavailability data) regarding the active ingredient of the generic product. In the event FDA discovers that relevant data are missing or discrepant, Pfizer requests that FDA take appropriate remedial action, including (if appropriate) suspension or withdrawal of ANDA approval.

B. Statement of Grounds

Background

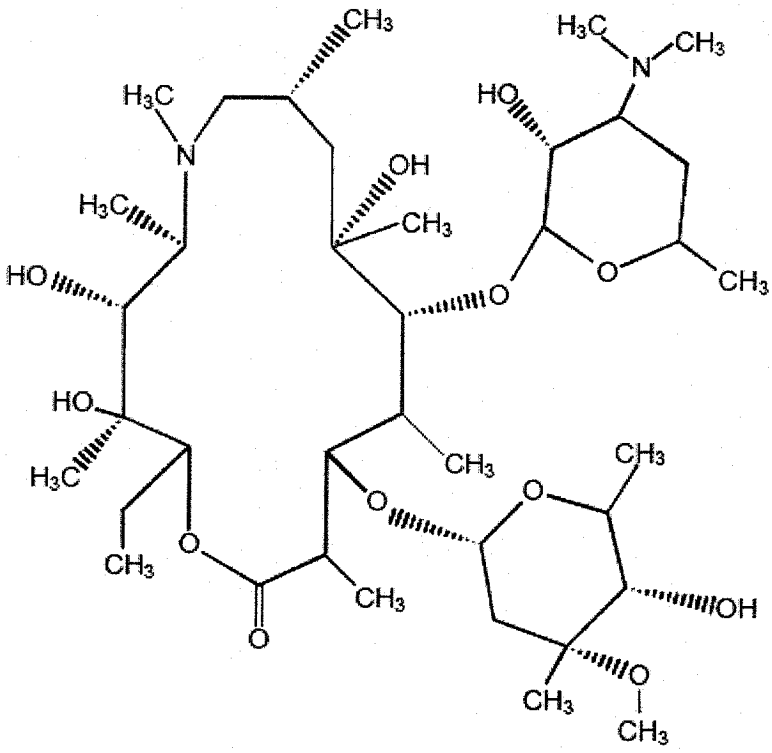
Zithromax® (azithromycin)

Pfizer is the New Drug Application ("NDA") holder for *Zithromax*®, an antibiotic that is indicated for the treatment of certain types of bronchitis and pneumonia, as well as for sinusitis and for ear infection. The active moiety in *Zithromax*® is azithromycin, which has a molecular formula of $C_{38}H_{72}N_2O_{12}$, and a molecular weight of 749.00 (anhydrous). Azithromycin has the following structural formula:

---

the incorporated solvent is water, the solvate is commonly known as a hydrate." FDA, Guidance for Industry, ANDAs: Pharmaceutical Solid Polymorphism, Chemistry, Manufacturing, and Controls Information, December 2004 ("Polymorphism Guidance"), at 2.

[2] We use the term "active ingredient" and "drug substance" interchangeably in this Citizen Petition in a manner consistent with FDA's use of the terms in its guidance documents, *e.g.*, Polymorphism Guidance.



Polymorphs of Azithromycin

The U.S. Pharmacopoeia ("USP") monograph for azithromycin identifies two polymorphic forms of the molecule: a monohydrate form (one molecule of water per molecule of azithromycin) and a dihydrate form (two molecules of water per molecule of azithromycin). As described in the USP monograph, azithromycin monohydrate has a molecular formula of $C_{38}H_{72}N_2O_{12}*H_2O$ and a molecular weight of 767.02. Azithromycin dihydrate has a molecular formula of $C_{38}H_{72}N_2O_{12}*2H_2O$ and molecular weight of 785.02. The USP monograph specifies that an azithromycin product should be labeled "to indicate whether it is the monohydrate or the dihydrate." USP Monograph, Attachment 1.

In addition to the two crystal forms described in the USP, a number of other specific forms of azithromycin have been identified to date. These polymorphs include several monohydrate forms that contain solvates in addition to the one water molecule per azithromycin molecule. A sesquihydrate form (Form G) also has been identified, which contains 1.5 water molecules per azithromycin molecule and has the molecular formula $C_{38}H_{72}N_2O_{12}*1.5H_2O$.

Pfizer's *Zithromax*® product contains azithromycin dihydrate. As required by FDA labeling regulations and the USP monograph, the FDA-approved product label for *Zithromax*® specifically discloses that the active ingredient of *Zithromax*® is azithromycin in its dihydrate form. The label states: "Zithromax is supplied for oral

administration as film-coated, modified capsular shaped tablets containing azithromycin dihydrate."

Generic Azithromycin for Oral Suspension Marketed by Pliva

Pliva holds an approved ANDA for generic azithromycin for oral suspension, and currently is marketing such a product. According to this product's label, the active ingredient contained therein is azithromycin "as the monohydrate." Pliva Label, Attachment 2.

Analytical tests run on samples of the Pliva azithromycin for oral suspension product indicate, however, that this product is not accurately labeled with respect to the polymorphic form of azithromycin it contains. Pfizer analyzed market samples of the Pliva (300 mg, 600 mg, 900 mg and 1200 mg) generic azithromycin for oral suspension product, using a combination of Fourier Transform Infrared Spectroscopy ("FTIR"), Powder X-Ray Diffraction ("PXRD"), ^{13}C Solid State NMR ("ssNMR"), Headspace gas chromatography ("GC") and gas chromatography-mass spectroscopy ("GC-MS"). The results of the tests were compared to data generated from reference materials of azithromycin sesquihydrate (Form G), azithromycin dihydrate (Form A), and other forms of azithromycin. The results demonstrate that the Pliva azithromycin for oral suspension product contains primarily azithromycin in the sesquihydrate form (Form G). Attachment 3.

Pfizer has no information on why the Pliva generic azithromycin for oral suspension product is inaccurately labeled with respect to the polymorph.[3] Pfizer also does not know whether the polymorphic form of azithromycin was incorrectly identified in the ANDA submitted for this product. Finally, Pfizer has no information on whether Pliva adequately assessed any impact that different polymorphic forms would have on the safety and efficacy of generic azithromycin.

The Misidentification of Azithromycin Polymorphs Raises Significant Concern

As FDA consistently has noted, differences in chemical and physical forms of an active ingredient may affect drug performance, including stability, dissolution, and bioavailability. Thus, FDA's ANDA and labeling regulations, and related guidances, require manufacturers to identify with particularity the chemical and physical form of a drug substance, including the specific solvate and hydrate polymorph, in the ANDA submission and the drug product label. FDA also has made clear that accurate identification and assessment of the polymorphic characteristics of an active drug substance are particularly important for generic drug products.

FDA's regulations governing the content of ANDAs incorporate by reference the chemistry and manufacturing information requirements that apply as well to

[3]Pfizer owns patents claiming azithromycin dihydrate and azithromycin sesquihydrate, but not azithromycin monohydrate.

NDAs. Pursuant to 21 C.F.R. §314.94(a)(9), an ANDA must contain the information outlined in 21 C.F.R. §314.50(d)(1). That provision requires drug applications to include "a full description of the drug substance *including its physical and chemical characteristics*" (emphasis added).

FDA's 2004 Polymorphism Guidance explicitly directs those preparing ANDA applications to focus on the chemical and physical forms of polymorphs of an active ingredient. FDA defines polymorph in this document to describe, among other things, solvate and hydrate forms:

> Polymorphic forms in the context of this guidance refer to crystalline and amorphous forms as well as solvate and hydrate forms . . . Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. If the incorporated solvent is water, the solvate is commonly known as a hydrate.

Polymorphism Guidance at 2.

As the Polymorphism Guidance makes clear, proper characterization of a drug polymorph is necessary to ensure effective regulatory review of manufacturing processes and drug performance:

> Polymorphic forms of a drug substance can have different chemical and physical properties . . . [which] can have a direct effect on the ability to process and/or manufacture the drug substance and the drug product, as well as on drug product stability, dissolution, and bioavailability. Thus, polymorphism can affect the quality, safety, and efficacy of the drug product.

Id. at 3.

The Polymorphism Guidance directs applicants to carefully characterize drug polymorphism, and refers applicants to the ICH Guidance, *Common Technical Document – Quality: Questions and Answers/Location Issues,* Section III.A.3.1 ("ICH Guidance") in order "to find the suggested placement of information related to the polymorphism that is important to include." Polymorphism Guidance at 2. The ICH Guidance, in turn, specifies where such information can be included in an ANDA for those submitting a document in the Common Technical Document format. ICH Guidance at §§3.2.S.1.3 - 3.2.S.4.5. The requested information includes: a list of polymorphic forms, a description of manufacturing process and controls established to ensure that the correct polymorph is produced, and studies performed to identify the potential polymorphic forms of the drug substance. *Id.*

Thorough analysis and explication of polymorphism is especially important in ANDAs that seek approval of generic products containing polymorphs that differ from the polymorph in the reference listed drug ("RLD"). As FDA made clear in a 2002 response to a citizen petition, the agency, in reviewing such a proposed generic drug, must make a scientific assessment that the polymorphism does not adversely affect

drug performance, compared to the RLD. Letter from FDA to Donald O. Beers et al., Docket No. 00P-1550 (February 15, 2002)

The Preamble to the Orange Book[4] reiterates this point, emphasizing that polymorphic forms can only be considered the same if there is scientific evidence demonstrating that their structures result in the same bioavailability and bioequivalence:

> Anhydrous and hydrated entities, as well as different polymorphs, are considered pharmaceutical equivalents and must meet the same standards and, where necessary, as in the case of ampicillin/ampicillin trihydrate, their equivalence is supported by appropriate bioavailability/bioequivalence studies.

Orange Book at xiii-xiv.

The need for specific review of polymorphic forms is thus clear. FDA consistently places the burden on the ANDA applicant to identify and characterize the polymorphic form of an active ingredient proposed for use in a generic formulation.

FDA Should Initiate a Recall of the Apparently Misbranded Pliva Generic Azithromycin for Oral Suspension Product

The FFDCA and FDA label regulations require that drug labels accurately and completely describe "the proprietary name and the established name of the drug," as well as the "chemical name and structural formula of the drug." 21 C.F.R. §§201.57(a)(1)(i) and (vi). This includes identifying the polymorph of the drug. As the USP monograph for azithromycin explicitly requires, the label for an azithromycin drug product must "indicate whether [the drug] is the monohydrate or the dihydrate." USP Monograph, Attachment 1. An azithromycin drug label that does not accurately identify the polymorph contained in the product is misbranded. *See* 21 U.S.C. §§352(a), (e), and (g).

The Pliva label identifies its generic azithromycin for oral suspension as containing "*azithromycin monohydrate* powder equivalent to 300mg, 600 mg, 900 mg or 12 mg azithromycin per bottle" Pliva Label, Attachment 2 (emphasis added).

In contradiction to these label statements, analytical tests conducted by Pfizer indicate that Pliva's azithromycin for oral suspension product contains primarily azithromycin in the sesquihydrate form (Form G) and minimal azithromycin in the monohydrate form. Attachment 3.

The Pliva azithromycin for oral suspension product is misbranded because its label does not correctly identify the polymorphic form of the active ingredient in the product. *See* 21 U.S.C. §§352(a) and (e). The product is also misbranded because it is not labeled in accordance with the USP monograph for azithromycin. *See* 21 U.S.C. §352(g).

---

[4] Approved Drug Products with Therapeutic Equivalence Evaluations (26th Ed., 2006) ("Orange Book").

FDA should initiate a recall so that inaccurate labeling of the Pliva azithromycin for oral suspension product can be removed and corrected. A recall will ensure that the misbranded product no longer misidentifies its active ingredient as being azithromycin monohydrate.

FDA Should Determine Whether the ANDA Submitted by Pliva is Defective and Thus Subject to Withdrawal

In addition to initiating a recall, FDA should review the Pliva ANDA for azithromycin for oral suspension to determine whether the polymorphic form of azithromycin was correctly stated, and whether appropriate testing was conducted to assess product performance characteristics, including stability, dissolution, and bioavailability.

As FDA notes in the Polymorphism Guidance, proper characterization of the chemical and physical properties of drug polymorphs is critical to review of drug product quality, safety, and efficacy. Polymorphism Guidance at 3. Moreover, such characterization is especially important when, as here, a generic drug contains a polymorph different from the polymorph contained in the RLD.

FDA should therefore thoroughly investigate the accuracy and completeness of the information provided by Pliva in its ANDA regarding the form of the azithromycin ingredient contained in its generic azithromycin product. FDA should take steps to withdraw the ANDA if such information is not correct or complete. *See* 21 U.S.C. §355(e); 21 C.F.R. §314.150(a)(2)(iv).

Withdrawal also may be appropriate if FDA determines that an ANDA mischaracterizes drug polymorphism, and that such mischaracterization reflects a lack of control over drug manufacturing. 21 U.S.C. §355(e)(5)(2). FDA should therefore investigate whether the manufacturing process for the Pliva product is "inadequate to assure and preserve the identity, strength, quality, and purity" of the generic azithromycin products. *Id.*

C. Environmental Impact

The petition requests that FDA review the applications to market generic azithromycin. Because the requested action would not increase the use of the active moiety, the petition is subject to a categorical exclusion from the requirement of an environmental impact assessment. *See* 21 C.F.R. §25.31(a).

D. Economic Impact

Information on the economic impact of this petition will be submitted if requested by the Commissioner.

E. Certification

Pfizer certifies, that, to the best knowledge and belief of Pfizer, this petition include all information and views on which the petition relies and that it includes representative data and information known to Pfizer which are unfavorable to the petition.

Respectfully submitted,

Jeffrey Chasnow
Emily Marden
Pfizer Inc
235 E. 42nd Street
New York, NY 10017