ARNOLD & PORTER

Donald O. Beers
Donald_Beers@aporter.com

202.942.5012
202.942.5999 Fax
555 Twelfth Street, NW
Washington, DC 20004-1206

7596 '01 JUN 5 P2:51

June 4, 2001

VIA FEDERAL EXPRESS
Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 10-61
Rockville, MD 20857

Re: Docket No. 00P-1550, Citizen Petition Relating to Cefuroxime Axetil

Dear Sir or Madam:

On behalf of our client, GlaxoSmithKline, we submit this additional statement in support of the above-referenced Petition. This statement relates to a proposed change[1] in the United States Pharmacopeia ("USP") monograph for cefuroxime axetil tablets that, we submit, demonstrates a fundamental point made in the original Citizen Petition submission dated September 29, 2000 — *i.e.*, that the introduction of crystalline forms into a cefuroxime axetil product, without very strict controls on crystallinity and polymorphic forms, presents an unacceptable risk of a product that will lack consistent bioavailability.

Background (for full details please refer to the original Petition submitted 9/29/00)

GlaxoSmithKline markets Ceftin® tablets, which contain two diastereoisomers of the active ingredient cefuroxime axetil in amorphous form. The Petition raises legal objections and product quality concerns associated with abbreviated new drug applications ("ANDAs") seeking approval to market generic products that contain, in part, crystalline forms of cefuroxime axetil. Different crystalline polymorphs exist for each diastereoisomer. Those polymorphs differ markedly from each other in solubility — and thus presumptively in bioavailability. Each crystalline form is, moreover, less soluble, and consequently less bioavailable, than the roughly 50:50 mixture of the two amorphous isomers that is found in the approved product and that conforms to specifications in the existing USP drug substance and drug product monographs.

SUP3

[1] A copy of the proposal, as published in the March-April 2001 *Pharmacopeial Forum*, is attached as Exhibit R.

00P-1550

We understand that a generic product would not be approved if the ANDA applicant could not produce at least one batch, used in the bioequivalence test submitted in its ANDA (the "biobatch"), that would fall within FDA acceptance criteria for bioequivalence. If there are not effective controls over amorphous-crystalline ratios and the precise mix of crystalline polymorphs, however, there is a significant risk that any given production batch of the generic would differ in bioavailability from the biobatch, and thus from the innovator product for which it might be substituted. Safety and effectiveness concerns attend this risk. In addition, increases in crystallinity in the active ingredient after manufacture are more likely in a product containing a mixture of amorphous and crystalline forms due to "seeding" of the amorphous materials. An increase in crystallinity after the manufacture of the product could change the mix of polymorphs present in the product and the overall ratio of amorphous-to-crystalline material — and thus bioavailability — during the shelf-life of the drug.

The Petition argues that cefuroxime axetil that is partially or totally in a crystalline form is not the same active ingredient as amorphous cefuroxime axetil. It also notes that the current USP drug substance monograph does not permit crystalline forms. Potential generic applicants have sought amendment of the drug substance monograph. An initial USP decision to grant that amendment is now on appeal to the USP Executive Committee.[2] This statement addresses a proposed amendment to a different but related USP monograph, that for cefuroxime axetil tablets.

Significance of Proposed Change to Tablet Monograph

There is now, we submit, evidence that at least one generic manufacturer is unable to produce cefuroxime axetil tablets that are adequately and consistently dissolved. That company's product is apparently unable to meet consistently the dissolution test included in the current USP monograph for cefuroxime axetil tablets. That company has, accordingly, petitioned USP to change the test.

[2] GlaxoSmithKline has opposed the change on quality grounds and was recently notified that Roger Williams, M.D., the Executive Director of the USP, has agreed to refer the matter to the USP's Executive Committee (of the Council of Experts) for further review. In so doing, Dr. Williams acted at the request of GlaxoSmithKline after hearing expert scientific presentations on the relevant product quality issues; these presentations included data and expert opinion previously submitted to this docket in support of the original Petition. The outcome of the Executive Committee's deliberations cannot be predicted at this time.

As explained in the original Citizen Petition submission of September 29, 2000, GlaxoSmithKline does not agree, at the threshold, that standard product performance testing (*e.g.*, dissolution testing) alone is adequate to control for potential variations in the solid-state form of cefuroxime axetil in formulations that include some proportion of crystalline drug substance. As noted in the expert declaration of Dr. Stephen Byrn[3], included as Exhibit E with the original Petition:

> [P]erformance testing, *e.g.*, conventional dissolution testing, is not adequate to contend with the complex solubility profile displayed by cefuroxime axetil and the associated potential variability in bioavailability. Given the complexities, the most appropriate means of assuring quality, efficacy, and product performance is to control directly for solid state form in the drug product and drug substance.

Byrn Declaration at ¶ 11. Nonetheless, to the extent that dissolution testing does have a role in helping to monitor and regulate the quality of cefuroxime axetil tablets, it must NOT be compromised.

We recognize that the generic manufacturer's biobatch, which may have been judged bioequivalent to the GlaxoSmithKline product, may have itself had a dissolution profile outside of the tolerances of the current USP test. That could, however, be accommodated by adjusting the tolerances for that test, if justified by appropriate data establishing a sufficient *in vitro/in vivo* correlation. The fact that the generic manufacturer is taking the alternative tack of seeking approval of a clearly less stringent alternative test reinforces the product quality concerns that lie at the heart of the original Citizen Petition submission.

The proposed alternative dissolution test differs from the current USP test in two potentially important respects: higher paddle speed and elimination of the 15-minute time

---

[3] Dr. Byrn is Professor and Head of the Department of Industrial and Physical Pharmacy at Purdue University and is currently Chairperson of FDA's Pharmaceutical Science Advisory Committee. He is the author of Solid-State Chemistry of Drugs. Recently, at the request of GlaxoSmithKline, he directed an intensive program of testing of cefuroxime axetil, keyed to the ICH Q6A Guidance, "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances." An overview of his work, and his conclusions and opinions about the importance of solid-state form to the quality and drug product performance of cefuroxime axetil, is presented in his written statement, which was — as noted above in the body of this statement — included with the original Petition submission as Exhibit E.

point. Each change conflicts directly with FDA's August 1997 "Guidance to Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms" (attached as Exhibit S).

The proposed change would increase the paddle speed from 55 rpm to 100 rpm. The Guidance says the following about paddle speed (at p. A-2):

> In general, mild agitation conditions should be maintained during dissolution testing to allow maximum discriminating power and to detect products with poor in vivo performance ... the common agitation (or stirring speed) ... with the paddle method ... is 50-75 rpm.

Thus, the proposed change, in the words of the Guidance, decreases the dissolution test's ability "to detect products with poor in vivo performance."

Similarly, the proposed elimination of the 15-minute time point, at which either 50% or 60% dissolution is required by the current test (depending on dosage strength), would also impair the ability of the test to characterize the quality of the product. Cefuroxime axetil is a poorly soluble, low permeability drug. As the FDA Guidance to Industry states unequivocally (at p. 6), "[f]or poorly water soluble drug products ..., dissolution testing at more than one time point for routine quality control is recommended to ensure in vivo product performance."[4]

Again, it is proposed that a safeguard "to ensure in vivo product performance" be deleted. Why are the proponents of generic products containing crystalline cefuroxime axetil proposing this adoption of a test that is less able to ensure *in vivo* performance? The answer is, we submit, obvious: Their product cannot consistently meet the existing, more discriminating test.

To reiterate, the danger is that, with partially crystalline content, and particularly without strict process, release, and stability testing and controls for solid-state form, a generic product may not produce consistently acceptable *in vivo* product performance.

---

[4] An alternative, not proposed by the generic applicants here, would be a dissolution profile (*id.*). See also, *id.* at 5. "[F]or slowly dissolving or poorly water soluble drugs (BCS class 2), a two-point dissolution specification, one at 15 minutes to include a dissolution range (a dissolution window) and the other at a later point (30, 45, or 60 minutes) ... is recommended to characterize the quality of the product."

The generic manufacturer's need to change the dissolution test underscores this concern. Thus, such a partially crystalline generic active ingredient cannot be considered the "same" active ingredient as amorphous cefuroxime axetil, and would, in any event, be unacceptable from a product quality standpoint.

GlaxoSmithKline has submitted comments to USP on the proposed dissolution test change, grounded in the same product quality concerns discussed above. So far as we are aware, no decision of any kind has been made on the published proposal.

Conclusion

The proposed changes to the dissolution test in the USP monograph for cefuroxime axetil tablets reinforce the product quality concerns raised in the original Petition by highlighting the distinct prospect of inadequate control over the solid-state form of cefuroxime axetil in formulations containing some proportion of crystalline material. Cefuroxime axetil in wholly or partially crystalline form should not be regarded as the "same" – as a matter of both law and product quality – as exclusively amorphous cefuroxime axetil. Accordingly, the above-referenced Petition should be, in all respects, granted.

Respectfully submitted,

Donald O. Beers
David E. Korn

Enclosure