

September 2, 2004

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OVERNIGHT DELIVERY**

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

**PETITION FOR STAY OF ACTION**

On behalf of Shire US, Inc., the undersigned submits this petition under 21 C.F.R. § 10.35 to request that the Commissioner of Food and Drugs stay the approval of any abbreviated new drug application (ANDA) for anagrelide hydrochloride capsules (brand name Agrylin®) until it has reviewed and responded to the Citizen Petition, dated August 13, 2004, submitted on behalf of Shire US, Inc. (Docket No. 2004P-0365).

*A. Decision involved*

On August 13, 2004, Shire submitted a Citizen Petition requesting that the Food and Drug Administration (FDA): (1) refrain from approving any ANDA for Agrylin capsules that fails to include active metabolite monitoring and bioequivalency testing; and (2) require an ANDA applicant for anagrelide hydrochloride capsules to evaluate bioequivalence, monitoring the active metabolite (3-hydroxy anagrelide) under both fed and fasting conditions. Shire holds pediatric exclusivity for Agrylin, which is set to expire September 14, 2004. Shire believes that FDA will approve an ANDA shortly thereafter, absent a review of and response to the Citizen Petition.

*B. Action requested*

Shire requests that FDA stay the approval of any ANDAs for anagrelide hydrochloride capsules until FDA reviews and responds to Shire's August 13, 2004 Citizen Petition (Docket No. 2004P-0365).

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*C. Statement of Grounds*

Shire believes that FDA should not approve any ANDAs for anagrelide hydrochloride capsules until it responds to Shire's Citizen Petition regarding Agrylin, because FDA's action on the Citizen Petition directly affects ANDAs for Agrylin. If FDA does not coordinate its actions on the Citizen Petition and such ANDAs, and FDA agrees with Shire, FDA could approve ANDAs that do not contain the required active metabolite monitoring. In such a case, a gap between the approval of an ANDA and FDA's decision on the Citizen Petition would exist. During this gap, approved ANDA holders would almost certainly place their products on the market. Shire is not aware of a remedy that FDA could impose to correct such a gap, once a generic drug product is on the market.

1. Regulations Applicable to Stay Decision

The mere filing of a citizen petition does not automatically stay the administrative action about which such a petition was filed. See 21 C.F.R. § 10.35(d). However, FDA will stay an administrative action if it determines that: (1) a stay or delay of the action is in the public interest; (2) a statute requires FDA to stay the action; or (3) a court orders FDA to stay the action. Id.

Under 21 C.F.R. § 10.35(e), FDA must grant a stay 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 petition has demonstrated sound public policy grounds supporting the stay; and
- (4) the delay resulting from the stay is not outweighed by public health or other public interests.

2. Shire's Petition Meets the Stay Criteria

FDA should not approve any ANDAs for anagrelide hydrochloride capsules until it responds to Shire's Citizen Petition. The delay requested is within the public interest, because the Citizen Petition merely requests that FDA ensure that ANDA applicants

demonstrate compliance with FDA's bioequivalence regulations. If FDA determines that, as Shire argued in its Citizen Petition, an ANDA applicant must demonstrate bioequivalence with the active metabolite, delaying the approval an ANDA until bioequivalence is evaluated is consistent with FDA requirements. Ensuring compliance with the bioequivalence regulations falls squarely within the public's interest.

Shire's request for a delay also meets the mandatory requirements for a stay. Shire will be irreparably harmed if FDA approves an ANDA but subsequently agrees with Shire's Citizen Petition. If FDA does not grant the requested delay, Shire believes that FDA will have little recourse once final approval is granted to an ANDA on September 15.

Shire's petition for a stay is not frivolous and is being pursued in good faith. Shire submitted its Citizen Petition to FDA on August 13, 2004. Shire made FDA aware of the active metabolite monitoring issue several months ago, as soon as it understood the effects of the active metabolite (3-hydroxy anagrelide). As outlined above, Shire requests that FDA act on the Citizen Petition before granting approval for an ANDA for Agrylin.

Shire's Citizen Petition and the requested stay are supported by sound public policy grounds. The Citizen Petition and this stay merely request FDA to ensure that any generic version of Agrylin is bioequivalent to Agrylin. FDA's bioequivalence regulations are designed to encourage the sale of generic drug products that have proven themselves to be as safe and effective as the reference listed drug. Therefore, Shire's request is supported by the public health grounds that serve as the foundation of FDA's bioequivalence regulations.

Moreover, any delay resulting from the stay is not outweighed by public health or other public interests. Shire appreciates the benefits of the availability of generic drugs. However, in this case, FDA must grant the stay to carefully review the Citizen Petition to ensure the integrity of the ANDA approval process and to avoid potential safety and efficacy concerns that might arise if ANDA approval is granted without adequate bioequivalency demonstration.

For the reasons outlined above, Shire requests that FDA grant a stay and delay approving any ANDA for Agrylin until it has taken final action on Shire's Citizen Petition.

Respectfully submitted,



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