

## **Barr Laboratories, Inc.**

---

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

October 20, 2004

Division of Dockets Management  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane  
Room 1061 (HFA-305)  
Rockville, MD 20852

### **COMMENTS TO DOCKET NO. 2004P-0365:**

On behalf of Barr Laboratories, Inc., the undersigned submits the following comments in response to the August 13, 2004 Citizen Petition submitted by Arnall Golden Gregory, LLP on behalf of Shire US, Inc. (Docket No. 2004P-0365). The Citizen Petition requests the Commissioner of FDA to: (1) refrain from approving any abbreviated new drug application (ANDA) for Agrylin® (anagrelide hydrochloride) capsules that fails to include active metabolite monitoring in bioequivalency testing; and (2) require an ANDA applicant for anagrelide hydrochloride capsules to evaluate bioequivalence, monitoring the active metabolite under both fed and fasting conditions.

On September 8, 2004, Mylan Pharmaceuticals, Inc. responded to Shire's Citizen Petition by requesting that it be denied (2004P-0365 C1). Barr acknowledges and supports Mylan's request that Shire's petition be denied and provides additional information herein supporting this position.

Barr Laboratories believes that the actions requested in Shire's August 13, 2004 Citizen Petition (Docket No. 2004P-0365) are without merit and should be denied immediately for the following reasons:

1. The Citizen Petition fails to present adequate justification for the proposed requirements for bioequivalence evaluation of anagrelide, which would serve only to put undue burden on ANDA applicants without providing any public health benefit. In fact, the resultant delays in approval of generic equivalents would be substantial, and would only serve to deny less fortunate patients access to safe, effective, and affordable treatment.
2. Shire, in its Citizen Petition, fails to propose any real or hypothetical biopharmaceutical mechanism that could result in clinically significant differences in metabolite concentrations arising from two anagrelide formulations demonstrated to be bioequivalent with respect to the parent drug.

2004P-0365

C2

3. Shire's demands are based entirely upon the unsupported premise that plasma concentrations of 3-hydroxy anagrelide could somehow be more sensitive to formulation differences than would plasma concentrations of the parent drug, anagrelide. This would be the only way that two formulations shown to be bioequivalent with respect to anagrelide could possibly yield clinically meaningful differences in plasma concentrations of 3-hydroxy anagrelide. Nowhere does Shire present any evidence that plasma concentrations of 3-hydroxy anagrelide are more sensitive to formulation differences than are plasma concentrations of anagrelide.
  - Shire's food effect data for the parent and metabolite have no bearing on the *relative* sensitivity of parent drug and 3-hydroxy metabolite to formulation differences.
  - Similarly, Shire's steady state plasma concentration data for parent drug and metabolite similarly have no bearing on the *relative* sensitivity of parent drug and 3-hydroxy metabolite to formulation differences.
4. The relative exposure of anagrelide and 3-hydroxy anagrelide is unremarkable in comparison to some well-known parent drug-active metabolite combinations, such as fluoxetine/norfluoxetine, amiodarone/desethylamiodarone, pentoxifylline/metabolites, buspirone/1-pyrimidinylpiperazine (1-pp), and hydroxychloroquine/metabolite, for which only the comparison of the parent drug profiles are required by FDA for the determination of bioequivalence.
5. Shire states misleadingly in its Citizen Petition "For several compounds with active metabolites, FDA has issued specific guidance relating to the design of bioequivalence studies (e.g., tolmetin, guanabenz, selegiline, diltiazem and terfenadine), and FDA required their measurement" [Citizen's Petition, page 13, second paragraph]. The product-specific bioequivalence study guidances cited by Shire date back as far as 1989, have long been obsolete, and no longer reflect the current thinking of the Agency as described in its current (March 2003) guidance entitled "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations". A review of the Summary Basis of Approval (SBOA) packages that are available for the products listed by Shire provides clarification on the specific requirements for these products:

## Barr Laboratories, Inc.

---

- Tolmetin bioequivalence studies have been approved, solely on the basis of parent drug assay (ANDA 74-729).
  - Guanabenz bioequivalence studies have been approved, solely on the basis of parent drug assay (ANDA 74-517).
  - Selegiline bioequivalence studies have been conducted with the assay of parent drug and active metabolites (ANDA 74-912). However, it is generally known for this product that due to low levels of the parent drug bioequivalence determination may not be feasible without comparison of metabolite levels.
  - Diltiazem bioequivalence studies have been conducted with the assay of parent drug and active metabolite (ANDA 74-943). In this ANDA, the parent drug and metabolite showed comparable formulation effects.
  - Terfenadine bioequivalence studies have been conducted with the assay of parent drug and active metabolite (ANDA 74-475). In this ANDA, the parent drug and metabolite showed comparable formulation effects.
6. The scientific consensus regarding the role of metabolites in bioequivalence studies has recently been presented in a review paper (Andre J. Jackson, Gabriel Robbie and Patrick Marroum. Metabolite and Bioequivalence: Past and Present, Clin. Pharmacokinet 2004; 43 (10): 655-672, copy attached). This paper concludes that "It is an accepted fact by many scientists in the pharmaceutical field that in most cases the assessment of bioequivalence of two different formulations can be based solely on the parent compound. This is because the parent compound is the entity most sensitive to formulation differences." This is consistent with Barr's experience conducting bioequivalence studies with a wide variety of chemical entities.
7. For bioequivalence comparisons of products for which the parent drug concentrations can be reliably measured, the Agency's guidance at most recommends measurement of the metabolite "to provide supportive evidence". As with all guidances, this recommendation is binding on neither the Agency, nor the Sponsor of an ANDA. There is no regulation requiring measurement of 3-hydroxy anagrelide in bioequivalence studies, nor does the Agency's guidance even recommend applying confidence interval criteria to metabolites (unless the parent drug cannot be measured reliably, which is not the case for anagrelide). Thus, per the Guidance, given reliable parent concentration data, metabolite data are never recommended for use as pivotal evidence of bioequivalence, only supportive evidence.

**Barr Laboratories, Inc.**

---

8. The extreme difficulty that Shire encountered in its attempts to synthesize miniscule quantities of 3-hydroxy anagrelide for use as a bioanalytical reference standard underscores the tremendous burden that a generic applicant would face if it were required to measure 3-hydroxy anagrelide in bioequivalence study plasma samples, as the generic applicant would necessarily have to synthesize its own reference standard. Furthermore, due to the age of any existing plasma samples from bioequivalence studies already conducted by generic sponsors, it would almost certainly be necessary to conduct new bioequivalence studies in order to meet Shire's extraordinary and unjustifiable demands. Repeating such studies to confirm what is already known would constitute unnecessary human experimentation.

To the best of the knowledge, information, and belief of the undersigned, the statements made in this submission are true and accurate.

Respectfully submitted,



Nicholas Tantillo  
Senior Director, Regulatory Affairs  
Barr Laboratories, Inc.

cc: Gary Buehler, Director, OGD  
Lawrence Yu, Ph.D., Deputy Director for Science, OGD