

August 13, 2004

Via Overnight Delivery

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

CITIZEN PETITION

On behalf of Shire US, Inc. (Shire), the undersigned submits this petition under section 505 of the Federal Food, Drug, and Cosmetic Act (the FDC Act), 21 U.S.C. § 355, and 21 C.F.R. §§ 10.30 and 314.94, to request the Commissioner of Food and Drugs (hereinafter referred to as "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.

As explained below, Shire believes that FDA cannot approve an ANDA for Agrylin without the applicant demonstrating that its product results in comparable exposure to the reference listed drug's active metabolite, 3-hydroxy anagrelide, seen after Agrylin administration. Without such a demonstration, an ANDA applicant simply cannot unequivocally state that their product is bioequivalent to Agrylin.

A. Actions Requested

The undersigned requests that:

- (1) FDA refrain from approving any ANDA for anagrelide hydrochloride capsules that fails to include active metabolite monitoring in bioequivalency testing. Specifically, FDA must require all ANDA applicants to monitor 3-hydroxy anagrelide in any bioequivalency study of anagrelide to ensure that a similar exposure to the active metabolite is achieved; and

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- (2) FDA require any ANDA applicant for anagrelide hydrochloride capsules to monitor the active metabolite *under both fed and fasting conditions*, because it appears that food affects a patient's exposure to the parent drug (i.e., the active ingredient) and active metabolite in different ways.

FDA must reject an ANDA that fails to provide the aforementioned monitoring and related assurances of bioequivalence and to avoid potential safety and efficacy concerns, because the ANDA will fail to satisfy the statutory and regulatory requirements for approval. Without such assurances, the ANDA product cannot be considered to be the same as the innovator drug.

B. Statement of Grounds

1. Background

FDA approved a new drug application for Agrylin 0.5mg and 1mg capsules on March 14, 1997.¹ The active ingredient in Agrylin is anagrelide hydrochloride (6,7-Dichloro-1, 5-dihydroimidazo [2,1-b]-quinazolin-2 (3H)-one hydrochloride monohydrate). Anagrelide hydrochloride is a highly potent and selective platelet lowering agent.

Agrylin is a prescription drug product indicated for the treatment of patients with thrombocythemia, a condition characterized by elevated blood platelets. Agrylin is used to reduce elevated platelet counts and the risk of thrombosis. Agrylin is also indicated for the amelioration of associated symptoms, including thrombo-hemorrhagic events.² FDA has designated Agrylin as the reference listed drug for anagrelide hydrochloride capsules.

Under the Orphan Drug Act, FDA granted Agrylin orphan drug exclusivity, which was set to expire on March 14, 2004. However, pursuant to section 505A of the FDC Act, 21 U.S.C. § 355a, and in accordance with FDA's Pediatric Written Request, Shire conducted a clinical trial that included a pediatric population, and obtained an additional six months of pediatric exclusivity for Agrylin. Therefore, Agrylin's exclusivity expires September 14, 2004.³

¹ Roberts Pharmaceutical Corp. obtained the NDA approval and was subsequently acquired by Shire.

² A copy of the approved package insert is included as Attachment A.

³ A copy of the relevant sections relating to Agrylin from FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (commonly referred to as "The Orange Book") is Attachment B.

During Shire's recent clinical trial that included both adult and pediatric populations, the company established for the first time in the target patient population (i.e., essential thrombocythemia [ET] patients) the pharmacokinetics of the major metabolite of anagrelide, 3-hydroxy anagrelide. Earlier *in vitro* studies had demonstrated that the metabolite was equipotent with the parent molecule in its potential platelet lowering activity, and was forty times more potent as a phosphodiesterase III (PDE III) inhibitor and, thus, as a cardioactive agent. However, this patient study showed for the first time that plasma exposure to the active metabolite was more than twice that of the parent drug. The greater plasma exposure to the active metabolite indicates that the active metabolite is a major contributor to the efficacy and safety of Agrylin.

Shire also conducted a clinical pharmacokinetic study to investigate the effect of food on the disposition of the parent drug and active metabolite. The results of this study showed that food affected the pharmacokinetics of the active metabolite and the parent drug (anagrelide) differently.

On March 11, 2004, Shire submitted a supplemental NDA (sNDA) in response to the FDA's Pediatric Written Request. The sNDA included the aforementioned clinical study in pediatric and adult ET patients (and other myeloproliferative disorders (MPD)), and information on the 3-hydroxy anagrelide metabolite. Based on this submission, FDA's Division of Gastrointestinal and Coagulation Drug Products granted a 6-month extension of exclusivity for Agrylin. The sNDA's proposed pediatric labeling changes are still under review by the Division.

Shire submitted another sNDA on June 17, 2004, to incorporate additional changes to the labeling based on Phase 1 clinical interaction studies and information in Special Patient groups (i.e., renally and hepatically impaired subjects). The submitted information included data on the pharmacokinetics of 3-hydroxy anagrelide metabolite. The proposed labeling changes include amendments to the safety portions of the labeling (e.g., PRECAUTIONS, WARNINGS). The NDA review division has not yet completed its review of this sNDA.⁴

Shire has also notified FDA's Office of Generic Drugs (OGD) of the changes proposed to the labeling based on the metabolite, including those changes affecting the safety portions of the labeling. Additionally, Shire has provided OGD documentation justifying the monitoring of anagrelide's active metabolite in any bioequivalency study through controlled correspondence; the cover letter for this correspondence is included in Attachment C.

⁴ Shire considers the contents of the sNDAs, not yet approved by FDA, to be proprietary and confidential and not subject to public disclosure at this time. Therefore, we are not attaching them to this Citizen Petition.

2. Historical Context

The initial qualitative identification of 3-hydroxy anagrelide as a human metabolite of the drug occurred two years ago. However, difficulties experienced in the synthesis of the metabolite precluded the conduct, reporting, and submission of clinical pharmacokinetic data on the active metabolite to FDA until earlier this year.

Beginning in 2001, Shire conducted additional nonclinical and clinical studies on anagrelide to meet certain regulatory requirements of the European Medicines Agency (EMA). It was during the course of these studies that Shire identified a new major metabolite of anagrelide. However, its subsequent chemical synthesis proved challenging. Initially, only small quantities of metabolite were available, enabling limited *in vitro* screening. In late 2002, the results of this screening showed the compound to be a highly potent PDEIII inhibitor and to possess comparable platelet-lowering potency to the parent drug.

However, the complexity of the chemical synthesis of the active metabolite delayed the availability of larger quantities of metabolite. Once larger quantities were available in early 2003, Shire initiated the conduct of *in vivo* whole animal studies to confirm, for example, the cardiovascular consequences of this PDEIII inhibition. In parallel, Shire established a clinical bioanalytical method for the metabolite, and clinical pharmacokinetic studies ensued.

As soon as practical, in third quarter 2003, Shire initiated analysis and reporting of the clinical pharmacokinetic study data. The company commenced the first patient study shortly thereafter. The above described data were necessary for Shire to fully determine the metabolite's contribution in man. Shire submitted results of the clinical study in adult and pediatric patients to FDA in the March 2004 sNDA.

In early 2004, Shire completed a definitive cardiovascular pharmacology study on anagrelide's active metabolite in the anesthetized dog model. The study demonstrated the qualitative comparability of the 3-hydroxy anagrelide to the reference positive inotrope milrinone, although 3-hydroxy anagrelide was 10-20 times more potent. Milrinone is a cardiostimulant used clinically in the treatment of congestive heart failure. However, such use requires careful monitoring in view of its profound effects on the cardiovascular system and consequential safety concerns. Similarly, monitoring of exposure to 3-hydroxy anagrelide from any new generic formulation of anagrelide should be undertaken to provide assurance that there is not an unexpected exposure to this cardiostimulant metabolite of anagrelide.

Shire has acted with due diligence. Despite the technical challenges relating to the chemical synthesis of the active metabolite, the company has provided FDA with the relevant clinical data on the metabolite as soon as practically possible.

3. Regulatory Overview

An ANDA must contain data demonstrating that the generic drug product is comparable or the "same as" the innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. See 21 U.S.C. § 355(j)(2)(A); 21 C.F.R. § 314.94(a).⁵ Therefore, an ANDA must contain the "same" active ingredient as the innovator drug and have essentially the same labeling. See 21 U.S.C. § 355(j)(2)(A). Further, a generic applicant must, with limited exception, scientifically show that its product is bioequivalent (*i.e.*, performs in the same manner as the innovator drug). See 21 U.S.C. § 355(j)(2)(A)(iv). FDA will refuse to approve an ANDA if the information in the application "is insufficient to show that the drug is bioequivalent to the listed drug." 21 U.S.C. § 355(j)(4)(F).

According to the FDC Act, an ANDA drug product is bioequivalent to a listed drug [one listed in FDA's Orange Book] if:

- (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); see also 21 C.F.R. § 320.1(e).⁶

⁵ All applicable statutory and regulatory citations are included in Attachment D.

⁶ The statutory and regulatory conditions to demonstrate bioequivalence are not exclusive and do not preclude other means of establishing bioequivalence. When the above methods are not applicable, other *in vivo* or *in vitro* test methods to demonstrate bioequivalence may be appropriate. In some cases, FDA may waive the bioequivalence testing requirement. See 21 C.F.R. § 320.22.

FDA states that bioavailability may be measured or bioequivalence “may be demonstrated by several *in vivo* and *in vitro* methods.” 21 C.F.R. § 320.24(a).⁷ Applicants must conduct “bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available” among those prescribed methods in the regulations. Id.

FDA lists, in relevant part, the following *in vivo* and *in vitro* approaches, in descending order of accuracy, sensitivity, and reproducibility, for determining the bioavailability or bioequivalence of a drug product:

(1) (i) An *in vivo* test in humans in which the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time. This approach is particularly applicable to dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution within the body; or

(ii) An *in vitro* test that has been correlated with and is predictive of human *in vivo* bioavailability data; or

(2) An *in vivo* test in humans in which the urinary excretion of the active moiety, and, when appropriate, its active metabolite(s), are measured as a function of time. The intervals at which measurements are taken should ordinarily be as short as possible so that the measure of the rate of elimination is as accurate as possible. Depending on the nature of the drug product, this approach may be applicable to the category of dosage forms described in paragraph (b)(1)(i) of this section. This method is not appropriate where urinary excretion is not a significant mechanism of elimination.

(3) An *in vivo* test in humans in which an appropriate acute pharmacological effect of the active moiety, and, when appropriate, its active metabolite(s), are measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility. This approach is applicable to the category of dosage forms described in paragraph (b)(1)(i) of this section only when appropriate methods are not available for

⁷ The FDC Act defines “bioavailability” as “the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.” 21 U.S.C. § 355(j)(8)(A); see also 21 C.F.R. § 320.1(a).

measurement of the concentration of the moiety, and, when appropriate, its active metabolite(s), in biological fluids or excretory products but a method is available for the measurement of an appropriate acute pharmacological effect. This approach may be particularly applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution.

21 C.F.R. § 320.24(b)(1)-(3).

FDA guidance states that applicants attempting to demonstrate bioequivalence to an active ingredient that is not highly soluble must do so using *in vivo* testing. 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). Attachment E. The standard *in vivo* bioequivalence study is conducted using a two-treatment crossover study design in a limited number of volunteers, typically 24-36 healthy adults. See The Orange Book, at ix. Attachment F. The study provides the rate of absorption, or bioavailability, of the generic drug, which the ANDA applicant can compare to the innovator drug.

Anagrelide is essentially unionized at physiological pH and is poorly water soluble (~1.5 ng/ml). Thus, according to FDA's guidance, anagrelide is not considered a "highly soluble" drug, because the maximum 1 mg dosage strength would not dissolve in the guideline-specified 250 ml of aqueous media. Therefore, a bioequivalence demonstration by a generic should be done using *in vivo* testing.

4. 3-Hydroxy Anagrelide is an Active Metabolite of Anagrelide Hydrochloride

Shire has demonstrated that 3-hydroxy anagrelide is an active metabolite of Agrylin capsules' active ingredient, anagrelide hydrochloride. Shire's recent studies show that 3-hydroxy anagrelide makes a meaningful contribution to the safety and efficacy of Agrylin. Furthermore, Shire's studies show that the active metabolite is generated during presystemic metabolism, which means that a patient's exposure to the active metabolite could be affected by changes in the drug formulation. The data supporting Shire's position in this Citizen Petition are summarized in Attachments G and H.

(a) *Evidence for meaningful contribution of anagrelide's metabolite to the efficacy and safety of the drug*

Anagrelide is extensively metabolized in man to two major metabolites; 3-hydroxy anagrelide and RL603. While RL603 has been shown to have no effect on megakaryocytopoiesis (and potentially, therefore, platelet lowering) (Erusalimsky, Hong,

and Franklin 2002), recent studies on 3-hydroxy anagrelide have revealed it to have significant and relevant pharmacology. Furthermore, results from a recent clinical pharmacokinetic study in ET and other MPD patients show plasma exposure to 3-hydroxy anagrelide exceeds plasma exposure to the parent drug (anagrelide) by 230%.

The effects of anagrelide and its metabolites on the differentiation of human CD34⁺ stem cells into megakaryocytes, which ultimately give rise to blood platelets, was assessed using a well established model of megakaryocytopoiesis (Cohen-Solal 1997, Cramer 1997). All referenced articles are provided in Attachment I. RL603 was found to be inactive in this model (Erusalimsky, Hong and Franklin 2002). By contrast, Shire found that 3-hydroxy anagrelide has a comparable potency to the parent drug, as evidenced by a similar *in vitro* concentration resulting in 50% inhibition (IC₅₀) of megakaryocyte growth/differentiation. The most marked effect of the metabolite, like anagrelide, was on cell growth. Results from several Shire studies indicated mean IC₅₀ values for effects on growth to be 27nM and compared to 48nM for effects on differentiation. (Attachment G, p. 7)

While anagrelide was already known to possess cardiovascular activity as the result of inhibition of PDEIII, the activity of its metabolites was only relatively recently determined. Shire found that anagrelide's active metabolite, 3-hydroxy anagrelide, was nearly forty times more potent as an inhibitor of PDEIII than anagrelide itself, having an *in vitro* concentration producing 50% inhibition (IC₅₀) of enzyme activity of 1.1nM. Shire confirmed these data in a second study that resulted in an average IC₅₀ of 0.9 nM (Attachment G, p. 8). The second study also revealed that the other metabolite, RL603, was an extremely weak inhibitor of PDEIII, with an IC₅₀ as high as 40,000nM.

Shire confirmed the expected *in vivo* cardiovascular activity of 3-hydroxy anagrelide in an anaesthetized dog model, where it was found to be 10-20 times more potent than the reference positive inotrope, milrinone, which it closely resembled with respect to its inotropic, chronotropic and vasodilatory activity. Thus, anagrelide's cardiostimulant activity, which manifests itself in side effects, such as tachycardia and palpitations, is likely due to the highly potent metabolite, 3-hydroxy anagrelide.

Therefore, based on the data summarized above and in Attachments G and H, Shire believes that the 3-hydroxy metabolite contributes significantly to Agrylin's pharmacological activity.

(b) *Evidence for presystemic metabolism*

A drug's formulation will only influence plasma exposure to an active metabolite when the metabolite is formed presystemically. As stated in recent FDA draft guidance, it is important to assess metabolite exposure in a bioequivalency study only when it is determined that the metabolite is formed presystemically. See "Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations" (July 2002); Attachment I.

Anagrelide has been shown to be quantitatively absorbed from the gastrointestinal (GI) tract, and is not chemically degraded within it. Therefore, anagrelide's oral bioavailability is determined only by presystemic metabolism. The absolute oral bioavailability of the drug will be a measure of the presystemic metabolism.

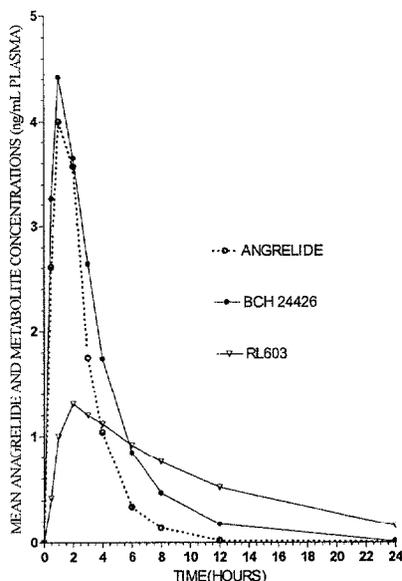
The unavailability of a clinical intravenous formulation of anagrelide has precluded the direct measurement of its absolute oral bioavailability. Nevertheless, other data provide valuable insight into the likelihood of presystemic metabolism of anagrelide.

(i) Data from healthy subjects (Attachment H, p. 5)

Shire conducted various clinical pharmacokinetic studies that have indirectly generated information on anagrelide's presystemic metabolism. Data from 38 healthy volunteers (age range 21-70, mean 52 years) who participated in three separate clinical pharmacokinetic studies demonstrated anagrelide to be rapidly absorbed (T_{max} of 1.3 hours).

Comparing the early concentration-time profiles of anagrelide and metabolite, the rate of formation of the 3-hydroxy anagrelide metabolite appeared to proceed in parallel with the absorption of the drug, suggesting that the metabolite's formation was effected by first-pass metabolism of anagrelide.

Figure 1: Plasma concentration time profile for anagrelide and its active metabolite, 3-hydroxy anagrelide (BCH24426), in man following a single 1 mg oral dose of the drug under fasting conditions



(ii) Studies in hepatically-impaired subjects (Attachment H, p. 5)

While gut wall or luminal metabolism can play a role, the most likely site of presystemic metabolism of a drug is the liver. An indication that the liver is involved in the biotransformation of anagrelide may be revealed by a comparison of anagrelide and metabolite exposure in normal and hepatically-impaired subjects.

Evidence that the liver plays a major role in the metabolism of anagrelide is supported by a pharmacokinetic study conducted in 10 subjects with moderate hepatic impairment. The study assessed the influence on the kinetics of both anagrelide and its metabolites. The study revealed an 8-fold increase in total exposure (AUC) to anagrelide. While part of this increase could be related to the 2.2-fold increase in half-life and a possible reduction in volume of distribution the increase also suggests that the liver plays a major role in the metabolism of anagrelide.

(iii) Oral clearance in the target patient population

Shire also recently investigated the pharmacokinetics of anagrelide and its metabolites in patients with ET and other MPDs. The study involved a comparison of younger patients (younger than 15 years of age) with a group of older patients.

Using the oral plasma clearance data, it is possible to estimate a drug's oral bioavailability. Furthermore, a drug's bioavailability is useful to measure a drug's presystemic metabolism, using the following equation:

$$F = 1 / (1 + (CL_b / F) / Q_H)$$

Where F = bioavailability
CL_b/F = oral blood clearance
Q_H = liver blood flow (assume 1.35L/min)

(Rowland & Tozer 1995). The equation assumes complete oral absorption and clearance only by the liver (Attachment H, p.6-9).

Previous studies, specific to anagrelide, demonstrate that the above equation can be used to estimate anagrelide's oral bioavailability. Two human radiolabelled studies on orally-administered anagrelide have shown that between 75-80% of the administered radioactivity is recovered in the urine; implying near quantitative absorption (Gaver et al 1981 and Shire study). Furthermore, investigation of the possibility for presystemic gut floral or gut wall metabolism has been investigated and ruled out (Attachment H, p. 7).

A recent partitioning study has shown a plasma to blood ratio of 1.2:1. Applying this to the calculation of bioavailability in a group of 18 ET patients results in a mean +/- estimate of bioavailability of 52.6% +/- 12.5 (Attachment H, p.9). As a result, at least 48% of an orally administered dose is likely to be metabolized during the drug's initial passage through the liver (i.e., presystemically).

A more detailed account of the evidence supporting the belief that anagrelide's active metabolite is formed by presystemic hepatic metabolism is contained in Attachment H.

In summary, Shire's data supports the conclusion that the active metabolite of anagrelide, 3-hydroxy anagrelide, is formed by first-pass metabolism. As such, its formation could be influenced by changes in drug product formulation.

5. Food Intake Affects Exposure to Agrylin and its Active Metabolite in Different Ways

Shire proposes that bioequivalency studies on anagrelide be conducted under both fed and fasting conditions and, equally important, that such studies measure both the drug and its active metabolite.

A recent food interaction study conducted by Shire demonstrated that food affects exposure to anagrelide and the active metabolite in different ways. In the presence of food, a later T_{max} value for anagrelide was observed with a small reduction in C_{max} (~14%), but an overall increase in AUC of approximately 20%. On the other hand, the active metabolite, 3-hydroxy anagrelide, while again showing a later T_{max} , demonstrated a more pronounced reduction in C_{max} (~30%), but did not experience a change in the overall AUC. The observed changes with food indicate that the relationship between anagrelide and its active metabolite, with respect to their exposure-time profiles, is not straightforward and that bioequivalence studies on anagrelide should include monitoring of its active metabolite in both fed and fasting states.

6. FDA's Guidances to Industry and the Agency's Past Actions Require an ANDA Applicant to Provide Data Demonstrating Comparable Exposure to the Active Metabolite Between the Listed Drug and the Generic Version

Shire's requests in this Citizen Petition are consistent with FDA's guidances to industry and past agency determinations in similar situations where the parent drug's active metabolite could influence assessment of therapeutic equivalence of products. Specifically, an ANDA applicant must provide data demonstrating comparable exposure to the active metabolite between the listed drug and the generic version.

(a) *General guidance*

In the aforementioned Draft Guidance (July 2002), FDA stated, regarding metabolite monitoring in bioequivalency studies:

For BE studies measurement of only parent drug released from the dosage form, rather than the metabolite, is generally recommended. The following are exceptions to this general approach:

A metabolite may be formed as a result of gut wall or other presystemic metabolism. If the metabolite contributes meaningfully to safety and/or efficacy, the metabolite and the parent drug should be measured. When the relative activity of the metabolite is low and does not contribute meaningfully to safety and/or efficacy, it does not need to be measured. We recommend the parent drug measured in these BE studies be analyzed using the confidence interval approach. The metabolite data can be used to provide supportive evidence of

comparable therapeutic outcome.

Draft Guidance, at Section VI, paragraph B; Attachment J.

In this Citizen Petition, Shire has presented data that shows: (1) 3-hydroxy anagrelide is equipotent with its parent, anagrelide, as a platelet reducing agent, (2) 3-hydroxy anagrelide is up to forty times more potent than its parent as a cardiovascular agent, and (3) plasma exposure to the active metabolite exceeds the plasma exposure to anagrelide in the target patient population by a ratio of greater than two to one. Furthermore, evidence is provided for the metabolite's formation by first-pass metabolism. Thus, anagrelide's active metabolite would appear to meet FDA's own criteria for metabolite monitoring.

(b) Compound-specific guidance

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. Guidance documents from Division of Bioequivalence, OGD, FDA; Attachment K. While no such guidance exists for anagrelide (information on the active metabolite has only just become available), the provision of such specific guidance for other compounds emphasizes the importance that FDA attaches to active metabolite monitoring.

7. Agrylin, Through Extensive Testing on Both Anagrelide and the Metabolite, is Safe and Effective, and Any ANDA Applicant for Anagrelide Must Conduct its own Testing to be Considered "The Same" as Agrylin Capsules

The FDC Act requires that a new drug be shown to be safe and effective. An ANDA product demonstrates that it is as safe and effective as the innovator drug by demonstrating that it is the "same as" the innovator, based on bioequivalence. Without data to demonstrate that the metabolite exposure of the ANDA applicant's product is comparable to the metabolite exposure from Agrylin, the ANDA applicant's product cannot be considered the "same as" the innovator's drug product.

Agrylin has undergone extensive testing to demonstrate that it is safe and effective. In the absence of the type of testing conducted by Shire and discussed in this Citizen Petition, an ANDA applicant will not be able to provide adequate assurances about any potential safety issues, such as the cardiovascular activity issue discussed above. Until such testing is performed, the ANDA applicant cannot demonstrate that its drug product is the "same as" Agrylin, such as the law requires. Although Shire will defer to FDA's

judgment on the type of testing that an ANDA applicant must perform, Shire believes that FDA must require ANDA applicants to perform such testing.

8. Conclusion

Under the FDC Act, FDA regulations, and relevant FDA guidance related to bioequivalence, a bioequivalency study of anagrelide hydrochloride must include specific data related to the active metabolite, 3-hydroxy anagrelide, and the effect of food on exposure of anagrelide and 3-hydroxy anagrelide. An ANDA for anagrelide hydrochloride that fails to include active metabolite monitoring under fed and fasting testing conditions cannot demonstrate meaningful bioequivalence and, thus, FDA must not approve any such ANDA.

For these reasons, FDA should require an ANDA applicant for anagrelide to monitor 3-hydroxy anagrelide in any bioequivalency study of anagrelide to ensure that a similar exposure to this active metabolite is achieved. In the absence of such assurances, an ANDA applicant cannot satisfy the statutory requirement of sameness to the innovator product.

C. Environmental Impact

As provided in 21 C.F.R. § 25.31, neither an environmental assessment nor an environmental impact statement is required.

D. Economic Impact

As provided in 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

The undersigned certifies, 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 petitioner which are unfavorable to the petition.

Respectfully submitted,

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