November 26, 2013

SigmaPharm
LABORATORIES

VIA FEDERAL EXPRESS

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

Dear Sir or Madam,

Sigmapharm Laboratories, LLC ("Sigmapharm") submitted to the FDA a Citizen Petition dated October 30, 2013. The Citizen Petition was submitted to consider incomplete and refuse to receive any ANDA for Asenapine Maleate Sublingual Tablets that does not contain the results of a bioequivalence study performed in accordance with the Agency's June, 2013 product-specific bioequivalence guidance for this drug product.

The submitted Citizen Petition was received by the FDA on October 31, 2013 and was assigned a docket number FDA-2013-P-1399/CP1, and was filed on 11/19/2013.

On November 26, 2013 Sigmapharm received a call from the FDA in reference to the above mentioned Citizen Petition to revise the "Certification" section of the Citizen Petition in accordance with 505(q) (1) (H) of Federal Food, Drug and Cosmetic Act.

We are therefore hereby submitting the revised Citizen Petition and requesting withdrawal of Citizen Petition dated October 30, 2013.

We sincerely apologize for the inconvenience caused. In case of any questions please direct correspondence to me per the contact information shown in the signature line.

Sincerely,

Rakesh Grover, Ph.D.
President & Chief Operating Officer,
Sigmapharm Laboratories, LLC
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FDA-2013-P-1554

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Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Dear Sir or Madam,

SigmapharmLaboratories, LLC ("Sigmapharm") submits this petition in quadruplicate under Section 505and 505 (q) of the Federal Food, Drug and Cosmetic Act ("FDCA" or the "Act) (21 U.S.C. § 355), 21 C.F.R. Part 314, and 21 C.F.R. § 10.30. Sigmapharm is a specialty pharmaceutical company engaged in the development, manufacture, and distribution of generic and innovator drug products in the United States. Below, Sigmapharm outlines its requested actions and relevant background information for the Agency's consideration and review.

A. Action Requested

Sigmapharm respectfully requests that the FDA consider incomplete and refuse to receive ("RTR") any Abbreviated New Drug Application ("ANDA")for Asenapine Maleate Sublingual Tablets that does not contain the results of a bioequivalence study performed in accordance with the Agency's June, 2013 product-specific bioequivalence guidance for this drug product.

Sigmapharm further requests that the filing acceptance dateof any ANDA for Asenapine Sublingual Tablets, for purposes of determining eligibility for 180-day exclusivity, be based on the date that the application firstcontained the results of a bioequivalence study performed in accordance with the Agency's June, 2013 bioequivalence guidance.

B. Statement of Grounds

August 13, 2013 was the first date on which the FDA could receive an ANDA for Asenapine Maleate Sublingual Tablets and it is believed that multiple ANDAs were submitted to

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the FDA on that date.The FDA must apply equitable standards in performing its preliminary filing acceptance review for these ANDAs and must RTR an ANDA that does not meet those standards. This is especially important for this drug product since any ANDA "received" by the FDA on August 13, 2013 will be eligible for a 180-day period of marketing exclusivity. This petition is focused on the standards that should be applied in determining whether the *in-vivo* bioequivalence study submitted in support of an ANDA for Asenapine Maleate Sublingual Tablets is sufficient to support FDA's receipt of the ANDA. Petitioner, Sigmapharm believes that one or more ANDAs submitted for this product contain bioequivalence studies that do not comply with the product-specific bioequivalence guidance issued by the FDA in June, 2013, (**ATTACHMENT A**) which represents FDA's standard for *in-vivo* testing of this product. Such ANDAs should be deemed insufficiently complete and an RTR letter should be issued to the ANDA sponsors. Furthermore, the FDA should not allow a firm to remedy (via the submission of a complying study[1]) a deficient ANDA that is awaiting the preliminary filing acceptance review, nor should the Agency accept a deficient ANDA and allow the sponsor to submit a complying study at a later date. Such allowances would be inequitable to sponsors who submitted a substantially complete ANDA, containing a complying study, on the NCE-1 date (as defined below). Relevant background information is presented below, and is followed by specific arguments in favor of the requested action.

1. Background:

a. Asenapine's NCE Status; Timing of ANDA Submissions and the 180-day Exclusivity Entitlement

Asenapine Maleate Sublingual Tablets are marketed under the trade name, Saphris® by Organon in dosage strengths of 5 mg and 10 mg. Saphris® was approved under NDA 022177 (owned by Organon/Merck) on August 13, 2009, for the treatment of schizophrenia. By virtue of its approved status and its listing in *Approved Drug Products with Therapeutic Equivalent Evaluations* (the "Orange Book") Saphris® is a "listed drug" which a company seeking approval of a generic version of the product may reference as the basis for its submission of an ANDA.

At the time of approval, Saphris® was granted a five year period of New Chemical Entity ("NCE") exclusivity, which is set to expire on August 13, 2014.The Federal Food Drug and Cosmetic Act prohibits the FDA from receiving an ANDA for any approved drug product that has been granted NCE exclusivity before that period of exclusivity has expired. There is one exception to this restriction. In cases where an ANDA applicant is seeking to challenge a patent listed in the Orange Book for the

[1] The term, "complying study" refers to a study that was performed in accordance with the Agency's June 2013 product-specific bioequivalence guidance for Asenapine Maleate Sublingual Tablets.

reference listed drug via the submission of a paragraph IV patent certification ("PIV certification") the FDA may receive the ANDA during one year that precedes the expiration date of the NCE exclusivity (the "NCE-1 date"). The first substantially complete ANDA received by the FDA which contains a PIV certification relative to a listed patent is eligible for 180-day period of marketing exclusivity, an entitlement that has the potential for significant financial return, upon commercialization of the product covered by the application. Since the earliest FDA receipt date for an ANDA for a product covered by NCE exclusivity is restricted by statute and requires a challenge to a listed patent, and since the first substantially complete ANDA received by FDA that challenges a listed patent is eligible for the coveted 180-day period of marketing exclusivity, there are typically multiple companies seeking to submit an ANDA on the NCE-1 date for a given listed drug. This is believed to be the case with Asenapine Maleate Sublingual Tablets.

b. OGD's ANDA Filing Acceptance Review

In order to discourage the practice of submitting substantively deficient ANDA's to the FDA for review, FDA's Office of Generic Drugs ("OGD") performs a preliminary review (the filing review) of each submitted ANDA to determinewhether it is sufficiently complete to warrant a critical technical review. If the application is deemed to be substantially complete, the date on which the application was initially received by the OGD is the filing acceptance date. If the application is deemed to be insufficiently complete, the OGD will RTR the application. The ANDA applicant may then amend the application to correct the deficiencies, or withdraw the application. If the application is amended to correct the deficiencies that resulted in the RTR, the OGD will consider the application to be a new original ANDA.[2] Thus the date on which the OGD received the amendment that resulted in the correction of the deficiencies would be considered the filing acceptance date. While the filing review is performed on every submitted ANDA, the outcome of this review is particularly critical for those ANDA's that contain a PIV certification because the date of receipt of such an ANDA for a given product, as determined by this review, is the determinant of the coveted, 180-day exclusivity entitlement.

The Agency recently issued aGuidance for Industry entitled, "ANDA Submissions – Refuse-to-Receive Standards", **(ATTACHMENT B)**which identifies serious deficiencies which may cause the FDA to RTR an ANDA. Notably the guidance states that serious bioequivalence deficiencies ranked first among the top categories of deficiencies that resulted in RTR actions for ANDAs submitted in 2012,

[2]The designation of such an application as a "new ANDA" occurred in association with the enactment of the Generic Drug User Fee Amendments (GDUFA).

accounting for 40% of all RTR actions.[3] This guidance further states that ANDA applicants should consult the bioequivalence recommendations webpage on FDA's website for product-specific guidance on conducting recommended *in-vivo* and/or *in-vitro* studies. Additionally, the guidance states, "*Submitting a non-recommended in-vivo study without justification will result in FDA's refusing to receive an ANDA.*"[4]

c. FDA's Issuance of a Product-Specific Bioequivalence Guidance for Asenapine

In June, 2013, the FDA issued a product-specific Bioequivalence Guidance for Asenapine Maleate Sublingual Tablets, and posted this guidance on its bioequivalence webpage. The timing of the guidance cannot be viewed as coincidental. It is obvious that the Agency was working towards issuing this product-specific guidance in advance of the (August 13, 2013)NCE-1 date.

Notably, the guidance calls for the conduct of a multiple dose, two-way crossover *in-vivo*bioequivalence study in schizophrenic patients who have been receiving a stable, twice daily dose of AsenapineMaleate, 10 mg, for a 3 month period. This is in contrast to the conventional, single-dose, two-way crossover *in-vivo*bioequivalence study in healthy subjects, which is typically required for an immediate release, solid oral dosage form. The requirement to utilize schizophrenic patients in the study as opposed to healthy volunteers was a measure intended to protect the safety of study subjects as discussed further in this petition and as recommended for pharmacokinetic studies involving antipsychotic drugs in a 2001 article by Cutler NR that was published in the Journal of Clinical Psychiatry.[5]Furthermore and very importantly as well, given the expected, substantially high drop-out rate due to adverse events, the use of patients as opposed to healthy subjects also serves to ensure the accuracy and reliability of information supporting FDA's bioequivalence determination for a given formulation of this product.

d. Sigmapharm's Experience with Asenapine*In-Vivo* Studies

Like other companies, Sigmapharm commenced development activities for our product with the goal of submitting our ANDA on August 13, 2013, while awaiting the issuance of a product-specific bioequivalence guidance. To that end, we

[3] Refer to the October 2013 Guidance for Industry entitled, "ANDA Submissions-Refuse to Receive Standards", Section II, lines 56-57.
[4] Guidance for Industry entitled, "ANDA Submissions-Refuse-to-Receive Standards," Section VII.B., lines 644-645.
[5]It has been previously acknowledged that due to differences in tolerability, bioequivalence studies of antipsychotic drugs should be performed in schizophrenic patients rather than in healthy volunteers. See Cutler NR. Pharmacokinetic studies of antipsychotics in healthy volunteers versus patients. J Clin Psychiatry. 2001;62 Suppl 5:10-3.

performed initial, pilot bioequivalence studies using a typical, three-way crossover design in which a single dose of the 10 mg product was administered to healthy volunteers under both fasted and fed conditions. During these studies, we observed an alarmingly frequent occurrence of adverse events, including bradycardia, extrapyramidal symptoms, and other events, which caused a verysubstantial percentage of enrolled subjects to drop out, thus prompting Sigmapharm to terminate these studies.Fortunately, the Agency issued the Asenapine bioequivalence guidance in June, 2013. This guidance obviated the safety issues that Sigmapharm observed during the conduct of its pilot studiesby requiring that a single, multiple dose *in-vivo* bioequivalence study be performed using schizophrenic patients, who have already been stabilized on the drug, as opposed to healthy subjects. While there was a limited period of time between the issuance of the guidance and the August 13, 2013 NCE-1 date, Sigmapharm was able to perform the requisite *in-vivo*bioequivalence study in full compliance with the guidance, and submit its ANDA on that date.

2. Arguments in Favor of Requested Action:

a. The FDA must apply consistent standard for ANDA filing acceptance

The Agency must apply consistent standards during the ANDA filing review process. This is especially important for ANDA's that contain a PIV certification and represent potential "first-filed" applications. If consistent standards are not applied, this could significantly disadvantage some ANDA applicants while affording a significant advantage to other applicants. This outcome would be inequitable and could carry significant and irreparablefinancial consequences.

b. FDA's June 2013 product-specific guidance is the established standard for demonstrating of bioequivalence for Asenapine Maleate Sublingual Tablets

FDA gave thoughtful consideration to the study design that would be required for this product when it issued its June 2013bioequivalence guidance for Asenapine Maleate Sublingual Tablets. Notably, the Agency addressed the recognized safety concerns associated with the administration of this product to healthy volunteers by requiring that the *in-vivo* bioequivalence study be performed in schizophrenic patients who have already been receiving a stable dose of the product. The timing of issuance of the Asenapine bioequivalence guidance cannot be viewed as coincidental. The Agency clearly intended to communicate its expectations to potential ANDA sponsors in advance of the August 13, 2013 NCE-1 filing date.

c. FDA's RTR Guidance States that the Agency will RTR an ANDA that contains a non-recommended study absent justification

FDA's October, 2013 Guidance for Industry entitled, "ANDA Submissions – Refuse-to-Receive Standards" articulates the standards that the Agency intends to apply in deciding whether to receive an ANDA.This guidance specifically states that ANDA applicants should consult the bioequivalence recommendations webpage on FDA's website for product-specific guidance on conducting recommended *in-vivo* and/or *in-vitro* studies. FDA's June, 2013 Asenapine bioequivalence guidance was posted on FDA's bioequivalence recommendations webpage and was available to all sponsors seeking to submit an ANDA for this product.

Additionally, the October, 2013 RTR guidance states, "*Submitting a non-recommended in-vivo study without justification will result in FDA's refusing to receive an ANDA.*" While the window of time between the issuance of the Asenapine bioequivalence guidance and the NCE-1 date was arguably very tight, this tight time period should not be viewed as appropriate justification for allowing ANDAs with non-complying studies to be deemed substantially complete for filing purposes.

d. ANDA sponsors had sufficient time to complete a complying *in-vivo*bioequivalence study prior to the NCE-1 date.

It was, indeed, possible to initiate and complete a complying study and submit an ANDA on the NCE-1 date, as was done by Sigmapharm. If Sigmapharm was unable to complete its study in time, our ANDA submission would have occurred at a later date. By submitting an ANDA with a complying study on August 13, 2013, Sigmapharm believes that it has earned the eligibility for the 180-day period of marketing exclusivity. Other ANDA sponsors who submitted an ANDA containing a complying study on August 13, 2013, should similarly be eligible for the 180-day period of marketing exclusivity.

C. Environmental Impact

Sigmapharmclaims a categorical exclusion from the requirement of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

D. Economic Impact

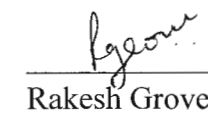
Sigmapharmwill, upon request by the FDA Commissioner, submit economic impact informationin accordance with21 C.F.R. § 10.30(b).

E. Certification

Sigmapharm makes the following certification pursuant to FDCA§ 505(q) (1) (H):

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that all representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: June 28, 2013 (knowledge of Asenapine Maleate product-specific bioequivalence guidance); August 13, 2013 (knowledge of ANDA submissions for Asenapine Maleate Sublingual Tablets on August 13, 2013 anticipated by virtue of NCE-1 date). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Sigmapharm. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



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Attachments:
A: Bioequivalence Guidance for Asenapine Maleate Sublingual Tablets
B: Guidance for Industry: ANDA Submissions- Refuse-to-Receive Standards