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February 25, 2014

***VIA ELECTRONIC SUBMISSION ONLY***
(www.regulations.gov)

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
HFA-305
Rockville, MD 20852

Re: **Docket FDA-2013-P-1623 – Comment on Sigmapharm Laboratories, LLC Citizen Petition (Amended Certification/Verification)**

Dear Sir or Madam:

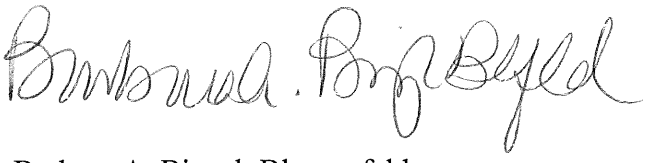
At the request of FDA, I am resubmitting the attached comments on Sigmapharm Laboratories, LLC's Citizen Petition regarding asenapine maleate. These comments were originally submitted on January 17, 2014 to the original Citizen Petition docket (Docket FDA-2013-P-1399), and resubmitted to the most current docket for Sigmapharm's amended Citizen Petition on January 30, 2014 (Docket FDA 2013-P-1623).

FDA informed me that the certification/verification statement in these comments required amendment to comply with the statutory requirements at 21 U.S.C. § 355(q)(1)(I). The attached comments are identical in all substantive respects to the comments previously submitted, other than amending the certification/verification statement, including today's date on the correspondence, and providing the current docket number in the Re: line with an explanation to the docket number changes in footnote 1.

* * * * *

Please consider the previous comments withdrawn, and replace them in Docket FDA-2013-P-1623 with the attached comments containing the amended certification/verification statement. Please contact me with any questions.

Respectfully submitted,



Barbara A. Binzak Blumenfeld

Attachment: Comments to Citizen Petition,
plus Attachment A

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Rockville, MD 20852

Re: **Docket FDA-2013-P-1623 – Comment on Sigmapharm Laboratories, LLC Citizen Petition**

Dear Sir or Madam:

We are providing these comments on the Citizen Petition ("Petition") first filed by Sigmapharm Laboratories, LLC ("Sigmapharm" or "the Petitioner"), dated October 30, 2013 (Docket FDA-2013-P-1399).[1] Sigmapharm requested that the U.S. Food and Drug Administration ("FDA" or "the Agency") take two specific actions: (1) consider incomplete and refuse to receive ("RTR") under the Draft RTR Guidance[2] any abbreviated new drug application ("ANDA") for asenapine maleate sublingual tablets that does not contain bioequivalence ("BE")

[1] Citizen Petition filed by Rakesh Grover, Sigmapharm Laboratories, LLC (October 30, 2013). FDA acknowledged receipt of the Petition on October 31, 2013, and noted that it was filed on November 19, 2013. Letter from Karen Kennard, FDA, to Rakesh Grover, Sigmapharm Laboratories, LLC (November 19, 2013). The Petitioner subsequently amended the certification statement and then corrected the amended certification statement, resulting in two new FDA dockets. The current (third) docket for the Citizen Petition with the corrected amended certification is now FDA-2013-P-1623.

[2] FDA, "Draft Guidance for Industry: ANDA Submissions – Refuse-to-Receive Standards" (October 2013), *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm121568.htm (hereinafter "Draft RTR Guidance").

data obtained using the study recommendations in the asenapine maleate Draft BE Guidance[3]; and (2) consider, for purposes of determining 180-day exclusivity, the filing acceptance date of any asenapine maleate sublingual tablet ANDA to be the date that the ANDA first contained bioequivalence data obtained from a study performed using the recommendations in the asenapine maleate Draft BE Guidance.[4]

For the reasons outlined herein, FDA must reject Sigmapharm's Petition. Sigmapharm raises safety issues and paragraph IV certification matters to obfuscate the real question: Must an ANDA sponsor use the proposed study design in a draft or final bioequivalence guidance document to demonstrate bioequivalence to the reference listed drug ("RLD")? The clear answer is no. FDA guidance documents – whether draft or final – are not legally binding. Contrary to the Petitioner's assertions, there are multiple ways to demonstrate that a generic drug is bioequivalent to the RLD, not merely the study design FDA proposes in draft or final guidance. The Petitioner ignores the fact that the regulations and FDA's historic, consistent interpretation of those regulations emphasize the need for studies that are sensitive enough to demonstrate a bioequivalence difference between the RLD and the proposed generic drug product, but do not dictate one particular type of study to do so.

Furthermore, FDA's RTR regulations do not require FDA to reject an ANDA that contains a bioequivalence study different than one proposed by FDA in a non-binding guidance document. The RTR regulations describe when the Agency may or will refuse to receive an ANDA based upon facial deficiencies of the application itself, but bioequivalence study design is not among the reasons listed. The Draft RTR Guidance – which was issued *after* the relevant ANDA filing dates at issue in this case – broadens the RTR regulations by stating that bioequivalence studies may differ from those FDA recommends when adequate justification is provided. There is no basis in the RTR regulations for concluding that a sponsor must provide adequate justification for its bioequivalence study design. Draft guidance has even less relevance than final guidance, and the legal validity of the Draft RTR Guidance is not established in either law or regulations. It merely represents a non-binding FDA policy that has not been vetted through notice and comment rulemaking.

Sigmapharm's Petition violates FDA regulations because it fails to include any information about the adverse events Petitioner observed during either its pilot bioequivalence study in healthy individuals or its pivotal studies in patient subjects that forms the basis for its Petition. Although Sigmapharm uses a purported safety issue as a means to cloud the real bioequivalence issue here, Sigmapharm nevertheless relies upon safety information to support its arguments. As a result, it must include the information supporting its position – including the pilot and pivotal study protocols, study reports, and details about the adverse events – in its

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[3] FDA, "Draft Guidance on Asenapine Maleate" (recommended June 2013), *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm (hereinafter "Draft BE Guidance").

[4] Petition, at 1.

Petition. By failing to do so, Sigmapharm has deprived both FDA and the public the opportunity to assess and comment on the underlying basis for its Petition.

Sigmapharm attempts further misdirection by claiming that the Draft RTR Guidance should be applied consistently yet extra-carefully in cases involving paragraph IV ANDAs because entitlement to the corresponding 180-day exclusivity period is at stake. If consistent application of guidance is important, then all ANDAs should be equally important. Whether an ANDA does or does not include a paragraph IV certification is not relevant to a bioequivalence determination.

Therefore, for the reasons explained further herein, FDA should deny Sigmapharm's Citizen Petition on the following three bases:

(1) Sigmapharm erroneously relies upon draft guidance as legally binding;

(2) Sigmapharm fails to recognize that there are multiple scientifically-valid ways to demonstrate that a proposed generic drug product is bioequivalent to the RLD; and

(3) Sigmapharm does not include the failed bioequivalence pilot study protocols, pivotal study protocols, study reports, adverse events details that form the basis for its arguments, in contravention of FDA regulations.

We first provide relevant background information regarding asenapine maleate and the submission of ANDAs for this drug product, as well as the issuance of the asenapine maleate Draft BE Guidance (Section I). We then provide justification for each of the legal bases on which FDA should deny Sigmapharm's Petition (Sections II-IV).

## I. BACKGROUND

### A. Asenapine Maleate

Asenapine maleate is a second-generation, atypical antipsychotic drug product. The first generation, "typical" antipsychotics were first developed in the mid-twentieth century to manage the positive symptoms of schizophrenia and to treat bipolar disorder. The typical antipsychotics were associated with numerous adverse events, including extrapyramidal symptoms and tardive

dyskinesia.[5] Examples of drugs in this class include Compazine® (prochlorperazine) and Thorazine® (chlorpromazine), among others.[6]

Because of these significant adverse effects, the second generation, "atypical" antipsychotics were developed. These newer antipsychotics generally have a lower risk of extrapyramidal symptoms, although they have their own associated adverse events both as a class and individually, including weight gain, effect on QTc interval prolongation, and metabolic issues.[7] Examples of the atypical antipsychotics include not only asenapine maleate (marketed as SAPHRIS®), but also Seroquel® (quetiapine fumarate), Abilify® (aripiprazole), and Zyprexa® (olanzapine).[8] Due to the nature of the underlying diseases, long-term patient compliance with a therapeutic regimen is difficult.[9]

Asenapine maleate is one of the newest atypical antipsychotic drug products, approved by FDA in 2009. Asenapine maleate has high affinity for several receptor types, including serotonin, dopamine, alpha 1 and 2 adrenergic, and histamine H1, and moderate affinity for histamine H2 receptors.[10] Because there is no affinity for muscarinic receptors, asenapine maleate does not cause anticholinergic effects or metabolic syndrome.[11] The drug is primarily absorbed in the oral mucosa, and absolute bioavailability for the sublingual route of administration is approximately 35%; however, if the drug is swallowed, the bioavailability is

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[5] Bishara D. and Taylor D., *Asenapine Monotherapy in the Acute Treatment of Both Schizophrenia and Bipolar I Disorder*, NEUROPSYCHIATRIC DISEASE AND TREATMENT 5:483-490 (2009), at 484; Balaraman R. and Gandhi H., *Asenapine, a New Sublingual Atypical Antipsychotic*, J. PHARMACOL. PHARMACOTHER. 1(1):60-61 (Jan-Jun 2010); Scarff J. and Casey D., *Newer Oral Atypical Antipsychotic Agents: A Review*, PHARMACY AND THERAPEUTICS 36(12):832-838 (December 2011), at 832.

[6] Other typical antipsychotic drug products include Haldol® (haloperidol); Loxitane® (loxapine succinate); Mellaril® (thioridazine hydrochloride); Moban® (molindone hydrochloride); Navane® (thiothixene); Orap® (pimozide); Prolixin® (fluphenazine hydrochloride); Stelazine® (trifluoperazine hydrochloride); and Trilafon® (perphenazine). FDA, "Information on Conventional Antipsychotics" (last accessed January 2, 2014), *available at* http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm107211.htm.

[7] Bishara and Taylor, at 484, 488; Balaraman and Gandhi; Scarff and Casey, at 836.

[8] Other atypical antipsychotic drug products include Clozaril® (clozapine); Fanapt® (iloperidone); Latuda® (lurasidone hydrochloride); Symbyax® (olanzapine/fluoxetine hydrochloride); Invega® (paliperidone); Risperdal® (risperidone); and Geodon® (ziprasidone hydrochloride). FDA, "Atypical Antipsychotic Drugs Information" (last accessed December 17, 2013), *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm094303.htm.

[9] *See, e.g.,* Gonzalez J., Thompson P., and Moore T., *Review of the Safety, Efficacy, and Side Effect Profile of Asenapine in the Treatment of Bipolar I Disorder*, PATIENT PREFERENCE AND ADHERENCE 5:333-341 (2011), at 334 (listing factors that cause noncompliance in individuals with bipolar disorder, including demographic factors; cognitive deficits; logistical life problems; poor understanding of the illness; negative attitudes towards medication; co-occurring substance abuse; minimal social support; and a poor quality doctor/patient relationship).

[10] Gonzalez, Thompson, and Moore, at 334.

[11] Balarman and Gandhi.

only approximately 2%. Peak plasma levels occur in 30-90 minutes, and the mean terminal half-life is approximately 24 hours. Steady-state concentrations with multiple dosing are achieved in three days.[12]

The atypical antipsychotics, including asenapine maleate, share certain common side effects, although patients may experience them to differing degrees. Several authors have examined and compared the side effects of the drug products in this class.[13] Asenapine maleate does, however, have one unique side effect: oral hypoesthesia, or reduced sensation in the oral cavity.[14] The SAPHRIS prescribing information highlights all of the asenapine maleate-associated side effects.[15]

B. ANDA Development and Issuance of Draft BE Guidance

1. *Asenapine Maleate ANDA Submissions*

FDA approved the SAPHRIS new drug application ("NDA") (asenapine maleate sublingual tablets; 5 mg and 10 mg)[16] on August 13, 2009 for both (1) the treatment of schizophrenia; and (2) the acute treatment of manic or mixed episodes associated with bipolar I disorder, as monotherapy or adjunctive therapy.[17] There currently is no approved ANDA, and SAPHRIS is the RLD. SAPHRIS received five-year new chemical exclusivity ("NCE"), which will expire on August 13, 2014.

Although the NCE has not yet expired, FDA may receive an ANDA in advance of this date. Under the Federal Food, Drug, and Cosmetic Act ("FFDCA" or "the Act"), FDA may

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[12] Scarff and Casey, at 835; Gonzalez, Thompson, and Moore, at 334; Citrome L., *Role of Sublingual Asenapine in Treatment of Schizophrenia*, NEUROPSYCHIATRIC DISEASE AND TREATMENT 7:325-339 (2011), at 326.

[13] Bishara and Taylor, at 488; Gonzalez, Thompson, and Moore, at 339; Balaraman and Gandhi; Citrome, at 334-336; Nierenberg A., *A Critical Appraisal of Treatments for Bipolar Disorder*, PRIM. CARE COMPANION J. CLIN PSYCHIATRY 12(suppl. 1):23-29 (2010).

[14] Balaraman and Gandhi.

[15] Adverse events associated with SAPHRIS at a $\geq$ 5% incidence and at least twice the level in placebo include: akathisia, oral hypoesthesia, and somnolence (when used to treat schizophrenia); somnolence, dizziness, extrapyramidal symptoms other than akathisia, and increased weight (when used as monotherapy to treat bipolar disorder); and somnolence and oral hypoesthesia (when used as adjunctive treatment for bipolar disorder). SAPHRIS Prescribing Information (revised March 2013), *available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

[16] NDA 22-177.

[17] SAPHRIS Prescribing Information (revised March 2013).

receive an ANDA up to one year prior to the NCE expiration date (*i.e.,* the "NCE-1" date)[18] when an ANDA sponsor challenges a patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book")[19] by filing in the ANDA a paragraph IV certification.[20] Therefore, in the case of asenapine maleate, FDA could have received one or more ANDAs containing a paragraph IV certification as early as August 13, 2013. Sigmapharm states that it submitted an ANDA with a paragraph IV certification on August 13, 2013, and that other sponsors likely did so as well.[21] Indeed, not only did our client submit such an ANDA with a paragraph IV certification, but so did at least one other sponsor.[22] As a result, multiple companies could share the 180-day exclusivity period reserved for the first ANDA(s) filed that contain a paragraph IV certification to a patent listed in the Orange Book.[23]

2. *Issuance of Asenapine Maleate Draft BE Guidance*

On June 20, 2013, FDA published a *Federal Register* notice announcing the availability of draft and revised draft product-specific bioequivalence guidance documents, including a new draft guidance for asenapine maleate.[24] The asenapine maleate Draft BE Guidance proposes one steady-state, multiple-dose, two-way, crossover *in vivo* study using 10 mg asenapine maleate in male and non-pregnant female patients who are already receiving 10 mg asenapine maleate twice daily for at least three months. FDA proposes no washout period, and that the studies be conducted with patients previously stabilized on the drug. The Agency provides additional recommendations for various bioequivalence study parameters, including patient entry criteria; safety monitoring; patient exclusion criteria; blood sampling; precautions and safety issues; statistical analysis of pharmacokinetic ("PK") data; and clinical reports/adverse reactions.

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[18] FFDCA § 505(j)(5)(F)(ii), *codified at* 21 U.S.C. § 355(j)(5)(F)(ii). We use the term "NCE-1" to denote the first possible date that FDA could receive an ANDA for asenapine maleate containing a paragraph IV certification (*i.e.,* August 13, 2013). This is the same designation used by the Petitioner.

[19] *Available at* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[20] FFDCA § 505(j)(2)(A)(vii)(IV), *codified at* 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

[21] Petition, at 3, 5.

[22] Comments filed by Winston & Strawn LLP addressing Sigmapharm's Petition (December 31, 2013) (hereinafter "Winston & Strawn Comments").

[23] FDA, "Guidance for Industry: 180-Day Exclusivity When Multiple ANDAs Are Submitted on the Same Day" (July 2003), *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064995.htm (hereinafter "180-Day Exclusivity Guidance"). In addition to five-year NCE, the Orange Book entry for SAPHRIS lists two other exclusivity periods that expired on September 2, 2013. It also lists two patents: 5,763,476 (expires June 9, 2020), and 7,741,358 (expires April 6, 2026).

[24] 78 Fed. Reg. 37230 (June 20, 2013).

Petitioner asserts that "[t]he timing of the guidance cannot be viewed as coincidental," and it is "obvious" that the Agency intended to release the Draft BE Guidance before the NCE-1 date.[25] Sigmapharm provides no support for this conclusion, and there are several reasons why the timing is not "obvious."

First, the Agency announced the availability of numerous product-specific bioequivalence guidance documents at the same time, and there is no reason to believe that FDA timed the announcement and release of multiple documents to coincide with one drug's NCE-1 date.[26] Second, FDA issues guidance documents under specific legislation, such as the Generic Drug User Fee Act ("GDUFA"). For example, in FDA's GDUFA performance goals and procedures, the Agency notes that it will identify "recommendations for draft guidances to clarify FDA recommendations with regard to complex product development and to help limit deficiencies in applications."[27] These guidances have nothing to do with specific drug products' NCE-1 dates. Finally, the Petitioner's assumption about the release of the guidance does not account for the complexities of the ANDA development process, which requires bioequivalence study design, institutional review board ("IRB") approval, study subject recruitment, study completion, and statistical analysis of the data. No company would wait until mere weeks before the NCE-1 date to begin its bioequivalence studies on the hope that FDA would release product-specific guidance. For all of these reasons, the Petitioner's bald assertion that the timing of the document release was "obvious" – without any justification or support for its assertion – must be disregarded.

## II. FIRST ARGUMENT: SIGMAPHARM ERRONEOUSLY RELIES UPON DRAFT GUIDANCE AS LEGALLY BINDING

### A. Regulations Promulgated through Notice and Comment Rulemaking are Binding, but Neither Draft nor Final Guidance Documents are Binding

Sigmapharm erroneously contends that the asenapine maleate Draft BE Guidance and the Draft RTR Guidance are binding on FDA and industry. The Petitioner plainly misunderstands the development, legal significance, and enforceability of guidance documents, and thus their difference from regulations promulgated through notice and comment rulemaking. Guidance

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[25] Petition, at 4, 6.

[26] *See, e.g.,* 78 Fed. Reg. 37230, 37230 (June 20, 2013) (noting that, in the development of product-specific bioequivalence recommendations, "draft recommendations are posted on FDA's Web site and announced *periodically* in the Federal Register" (emphasis added)).

[27] FDA, "Generic Drug User Fee Act Program Performance Goals and Procedures Fiscal Years 2013 through 2017" (posted July 17, 2012), *available at* http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm282513.htm, at 19. Guidance documents are also part of FDA's information technology plan under GDUFA. *See* FDA, "GDUFA Draft Information Technology Plan FY 2013-FY 2017" (December 2013), *available at* http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm379854.htm.

documents do not have the same legal effect as regulations – an axiom of administrative law. Congress and FDA have made this fact clear in numerous contexts.

The Administrative Procedure Act ("APA"),[28] the FFDCA,[29] and the Agency's procedural regulations[30] all address the development of regulations by notice and comment rulemaking. Historically, FDA has used other means to interpret Agency regulations and policies, including trade correspondence, formal and informal policy statements, and compliance policy guides, among others.[31] Recognizing the need for consistency, in 1997 FDA announced the availability of its good guidance practices ("GGPs") document.[32]

The GGPs set forth the basis for developing guidance documents and highlight their non-binding nature.[33] Congress used FDA's GGPs when it amended the Act to include a statutory provision on the development of informal Agency statements.[34] Subsequent to this change in the Act, FDA issued proposed[35] and final[36] regulations that conformed to the new statutory mandate and largely tracked the pre-statutory GGP document.

The GGP regulations define a "guidance document" as an FDA-prepared document for FDA staff, industry, and the public that describes FDA's interpretation of or policy on a regulatory issue.[37] The GGP regulations establish that guidance documents are non-binding, "do not establish legally enforceable rights or responsibilities," and may not include mandatory language implying a legal requirement (unless FDA is discussing a regulatory or statutory

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[28] 60 Stat. 237 (June 11, 1946).

[29] FFDCA § 520(d), *codified at* 21 U.S.C. § 360j(d).

[30] 21 C.F.R. § 10.40(d).

[31] FDA's historical development and use of such documents has been well-addressed. *See, e.g.,* Lewis K., "Informal Guidance and the FDA," 66 FOOD & DRUG L.J. 507 (2011).

[32] 62 Fed. Reg. 8961 (February 27, 1997).

[33] Guidance documents are distinguishable from "advisory opinions," which FDA established as a separate category of documents that are binding on the Agency. 21 C.F.R. § 10.85(e). Advisory opinions include *Federal Register* preambles (proposed or final regulations), trade correspondence, compliance policy guides (1968-present), and "other documents specifically identified as advisory opinions." 21 C.F.R. § 10.85(d)(1)-(4).

[34] Food and Drug Administration Modernization Act of 1997 ("FDAMA"), Pub. Law No. 105-115 (November 21, 1997), at 405; FFDCA § 701(h), *codified at* 21 U.S.C. § 371(h).

[35] 65 Fed. Reg. 7321 (February 14, 2000).

[36] 65 Fed. Reg. 56468 (September 19, 2000).

[37] 21 C.F.R. § 10.115(b)(1).

requirement).[38] The majority of guidance documents are "level 1"[39] and are first published in draft form; after the public has the opportunity to comment, then the final guidance document is prepared.[40]

Although guidance documents reflect FDA's current position on a regulatory matter, FDA *employees* may only depart from guidance if there is "appropriate justification and supervisory concurrence."[41] *Industry and the public* may use an alternative approach to the one recommended in the guidance document as long as it complies with the appropriate statutes and regulations.[42] Industry does not even have to discuss this alternative option with FDA beforehand.[43]

The Agency summarized the legal status of guidance documents most succinctly in the GGP final rule: "[b]ecause a guidance document represents the agency's current thinking on a subject but it is *not ever binding* on FDA or outside parties, *you should not rely on any guidance document*, draft or final" (emphasis added). Sigmapharm's argument that the asenapine maleate Draft BE Guidance must be followed is therefore legally incorrect. Guidance documents, whether draft or final, are non-binding and do not have the force and effect of regulations. Although courts have labored over the distinctions between substantive rules requiring notice and comment rulemaking and other Agency pronouncements that are excepted from rulemaking, courts have held that FDA cannot use guidance documents and other policy statements to circumvent the rulemaking process.[44]

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[38] 21 C.F.R. § 10.115(d), (i); FDA, Manual of Policies and Procedures ("MAPP") 4000.2, "Developing and Issuing Guidance" (revised September 13, 2005), *available at* http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/default.htm.

[39] Level 1 guidance documents include those that provide an initial interpretation of statutory or regulatory requirements; set forth more than minor changes in interpretation or policy; address complex scientific issues; or address highly controversial issues. 21 C.F.R. § 10.115(c)(1).

[40] 21 C.F.R. § 10.115(g)(1). For example, the Draft RTR Guidance document states prominently on its cover page, "[t]his guidance documents is being distributed for comment purposes only."

[41] FFDCA § 701(h)(1)(B), *codified at* 21 U.S.C. § 371(h)(1)(B); 21 C.F.R. § 10.115(d)(3).

[42] 21 C.F.R. § 10.115(d)(2).

[43] 65 Fed. Reg. 56468, 56471 (September 19, 2000) ("If you take an alternative approach, you are not required to discuss that approach with us.").

[44] *See, e.g.,* Community Nutrition Institute v. Young, 818 F.2d 943 (D.C.Cir. 1987) (holding that the Agency's use of "action levels" to regulate unavoidable food contaminants was illegal because notice and comment rulemaking procedures should have been followed); Becton, Dickinson and Co. v. FDA, 589 F.2d 1175 (2d Cir. 1978) (holding that FDA's interpretation of "restricted devices" as including "prescription devices" violated the Medical Device Amendments of 1976 because the Agency did not promulgate regulations); American College of Neuropsycho-Pharmacology v. Weinberger, No. 75-1187 (D.D.C. 1975), as republished in Kleinfeld V. *et al*, Federal Food, Drug,

B. FDA's Bioequivalence Regulations and RTR Regulations do not Require FDA to Take the Actions Sigmapharm Requests

Sigmapharm asserts that FDA should not receive any asenapine maleate ANDA not containing bioequivalence studies conducted using the proposed methods in the Draft BE Guidance. This position cannot be sustained for several reasons. First, the bioequivalence regulations provide for multiple ways to demonstrate bioequivalence so long as the most accurate, sensitive, and reproducible approach available is used. This position is further explained in Agency bioequivalence guidance documents. Second, the purpose of the RTR regulations is to determine which applications are facially deficient and must therefore be rejected. These regulations do not require that FDA refuse to receive an ANDA containing bioequivalence studies that differ from an FDA recommendation found in guidance. Finally, FDA's statement in the Draft RTR Guidance that "adequate justification" must be provided if a "non-recommended in vivo study" is submitted is not found in the RTR regulation, is not binding due to its guidance status, and is therefore not necessary for determining if an ANDA is deficient on its face. Comments submitted to the Draft RTR Guidance docket by the Generic Pharmaceutical Association ("GPhA") also request clarification of FDA's "adequate justification" statement.[45] For all of these reasons, FDA may receive an asenapine maleate ANDA so long as all information pertinent to demonstrating bioequivalence is provided in the application.[46]

1. *The Bioequivalence Regulations and Agency Guidance Permit Study Design Flexibility*

FDA's regulations[47] outline several alternate methods for determining bioequivalence,[48] although the sponsor must use the "most accurate, sensitive, and reproducible approach

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and Cosmetic Act Judicial Record 1975-1977. Washington, D.C.: Food and Drug Law Institute 1979:310-312 (granting a permanent injunction against the promulgation of regulations regarding administrative practices and procedures that were published in final form in the *Federal Register* without a proposed rule).

[45] GPhA comments (October 31, 2013), *available at* www.regulations.gov (docket FDA-2013-D-1120), at 7 ("GPhA asks the FDA to provide further clarification regarding its expectations for 'adequate justification' when an applicant proposes a study that does not confirm [sic] with a recommended testing approach.").

[46] FDA's "ANDA Filing Checklist" specifies the bioequivalence requirements for an ANDA submission, including information about the study, a statistical summary, and adverse events observed during the study. There is nothing to indicate that FDA assesses the details of why a sponsor chose a particular bioequivalence study type – just that the necessary bioequivalence information is provided. FDA, "ANDA Filing Checklist" (updated October 1, 2013), *available at* http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/Abbreviated NewDrugApplicationANDAGenerics/.

[47] The bioavailability and bioequivalence regulations were promulgated through notice and comment rulemaking, and are therefore binding requirements. *See, e.g.,* 40 Fed. Reg. 2615 (June 20, 1975) (procedures for determining the *in vivo* bioavailability of drug products – notice of proposed rulemaking); 40 Fed. Reg. 26164 (June 20, 1975) (procedures for establishing a bioequivalence requirement – notice of proposed rulemaking); 42 Fed. Reg. 1624

available."[49] The regulations present these options in descending order of sensitivity and therefore acceptability, including (1) a human *in vivo* test measuring PK parameters in an appropriate biological fluid as a function of time (or an *in vitro* test correlated with and predictive of *in vivo* bioavailability data); (2) a human *in vivo* test measuring urinary excretion of the active moiety or active metabolite over time; (3) a human *in vivo* test measuring an acute pharmacological effect of the active moiety or active metabolite over time; (4) appropriately-designed comparative clinical trials; (5) an *in vitro* test to measure *in vivo* bioavailability that is acceptable to FDA; or (6) "[a]ny other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence."[50]

FDA's guidance documents support this design flexibility and the non-absolute nature of FDA's bioequivalence study recommendations. For example, FDA notes that the bioequivalence recommendations for a particular drug product are based on the RLD's characteristics, the published literature, intra-Agency consultations, and Agency research.[51] Furthermore, public comments on a draft bioequivalence guidance document are considered before the document is finalized, and guidance may be revised at any time "to ensure that the most up-to-date BE information is available to the public."[52] These facts support the flexible and evolving nature of bioequivalence study recommendations.

Most importantly, FDA has recognized that it is not required to publish a product-specific bioequivalence guidance document at all before approving an ANDA. Rather, if FDA determines that the ANDA contains "sufficient evidence" to show that the proposed generic drug is bioequivalent to the RLD (and all approval requirements are met), then "FDA will approve the ANDA."[53] Therefore, if FDA can approve ANDAs without issuing *any* product-specific

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(January 7, 1977) (procedures for establishing a bioequivalence requirement – final rule); 42 Fed. Reg. 1638 (January 7, 1977) (procedures for determining *in vivo* bioavailability of drug products – final rule); 54 Fed. Reg. 28872 (July 10, 1989) (abbreviated new drug application regulations – proposed rule); 57 Fed. Reg. 17950 (April 28, 1992) (abbreviated new drug application regulations – final rule).

[48] 21 C.F.R. § 320.21(e).

[49] 21 C.F.R. § 320.24(a).

[50] 21 C.F.R. § 320.24(b)(1)-(6); *see generally* FDA, "Draft Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA" (December 2013), *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm121568.htm (hereinafter "ANDA BE Guidance"). We note that this ANDA BE Guidance revised and replaced two earlier FDA guidance documents. *Id.* at 1, fn. 2.

[51] FDA, "Guidance for Industry: Bioequivalence Recommendations for Specific Products" (June 2010), *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm, at 2.

[52] *Id.* at 3.

[53] *Id.*

bioequivalence guidance, then industry necessarily must have flexibility in designing these studies.

2. *The RTR Regulations and Draft RTR Guidance do not Require FDA to Refuse to Receive an ANDA Containing a Bioequivalence Study Other Than One Recommended by the Agency in Draft Guidance*

Sigmapharm argues that FDA's Draft RTR Guidance supports the Agency's refusal to receive any asenapine maleate ANDA containing bioequivalence studies that do not follow the recommendations in the Draft BE Guidance. Nothing in the Draft RTR Guidance supports this assertion. More importantly, the RTR regulations do not support Sigmapharm's argument. The RTR regulations are intended to help FDA decide which ANDAs are facially deficient and must not be received. An ANDA containing a bioequivalence study and all required supporting documentation are not facially deficient, and FDA would have no reason to refuse to receive the application. The Petitioner's argument must therefore be rejected.

The RTR regulations[54] were developed to determine if an ANDA or NDA is "sufficiently complete to permit a substantive review."[55] To conserve resources, FDA will refuse to receive an ANDA (or refuse to file an NDA[56]) that is not complete on its face. If an ANDA is not received, then the applicant may withdraw the application, amend it, or take no action (in which case it is not received).[57]

Although historically FDA permitted the submission of ANDAs containing a paragraph IV certification with a bioequivalence protocol but no bioequivalence data, FDA no longer permits such a practice.[58] If the ANDA does not contain "complete bioequivalence or bioavailability information at the time of its initial submission," FDA will not receive the

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[54] The RTR regulations were promulgated through notice and comment rulemaking and are therefore binding. *See, e.g.,* 47 Fed. Reg. 46622 (October 19, 1982) (new drug and antibiotic regulations – proposed rule); 50 Fed. Reg. 7452 (February 22, 1985) (new drug and antibiotic regulations – final rule); 54 Fed. Reg. 28872 (July 10, 1989) (abbreviated new drug application regulations – proposed rule); 57 Fed. Reg. 17950 (April 28, 1992) (abbreviated new drug application regulations – final rule); 59 Fed. Reg. 50338 (October 3, 1994) (abbreviated new drug application regulations; patent and exclusivity provisions – final rule).

[55] 21 C.F.R. § 314.101(a)(1), (b)(1).

[56] 21 C.F.R. § 314.101(a), (b). FDA has explained its reason for "filing" an NDA but "receiving" an ANDA. *See* 54 Fed. Reg. 28872, 28889 (July 10, 1989).

[57] 21 C.F.R. § 314.101(b)(3)(i)-(iii).

[58] 54 Fed. Reg. 28872, 28927 (July 10, 1989) (proposed 21 C.F.R. § 314.101(d)(8)); 57 Fed. Reg. 17950, 17959, 17965 (April 28, 1992).

application.[59] The *completeness* of the information submitted, however, does not address the *design* of the study.

The RTR regulations provide a list of circumstances in which FDA *may*[60] or *will*[61] refuse to receive an ANDA. For example, according to 21 C.F.R. § 314.101(d)(3), FDA may refuse to receive an ANDA if it does not contain "on its face" the information that is required to be in an ANDA per FFDCA § 505(j) or 21 C.F.R. § 314.94. Even if the design of a bioequivalence study were somehow pertinent to a facial determination about whether to receive the ANDA, the non-mandatory language in the regulation indicates that the Agency is not compelled to refuse to receive it, but may *choose* to refuse to receive it. FDA's 180-Day Exclusivity Guidance supports this fact, stating that the Agency will permit multiple first applicants "as long as the applications comply with applicable requirements for submission."[62]

The Draft RTR Guidance document, on the other hand, imposes new requirements that are not found in the regulations. The Draft RTR Guidance correctly encourages applicants to consult any product-specific bioequivalence recommendations that have been issued. However, FDA's further statement that FDA will refuse to receive an ANDA that contains a non-recommended *in vivo* study if the sponsor does not provide adequate justification impermissibly creates a new "requirement" that is not found in the RTR regulations. FDA's GGP regulations state that "FDA *employees* may depart from guidance documents only with appropriate justification and supervisory concurrence" (emphasis added),[63] but there is no parallel statement that *sponsors* must have "appropriate justification." Rather, a sponsor's alternative approach must comply with the statute and regulations.[64]

FDA is attempting to shift the burden for providing justification from the Agency to the ANDA sponsor. But even if the Agency must provide its own justification for deviating from the Draft BE Guidance (*i.e.,* reviewing a different bioequivalence study design), this is a secondary, substantive decision for FDA reviewers. The primary decision involves deciding whether the application is facially complete and can therefore be reviewed. Sigmapharm's reliance on the Draft RTR Guidance is therefore legally flawed – particularly because it was not

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[59] 57 Fed. Reg. 17950, 17965 (April 28, 1992).

[60] 21 C.F.R. § 314.101(d)(1)-(9).

[61] 21 C.F.R. § 314.101(e)(1)-(2).

[62] 180-day Exclusivity Guidance, at 4.

[63] 21 C.F.R. § 10.115(d)(3).

[64] 21 C.F.R. § 10.115(d)(2).

even available at the asenapine maleate NCE-1 date – a fact also noted by another commenter on this Petition.[65]

C. Conclusions

FDA must reject Sigmapharm's argument that the Agency cannot receive an asenapine maleate ANDA containing bioequivalence studies that differ from FDA's recommendations in draft guidance. Draft and final guidance documents are not legally binding, unlike regulations developed through notice and comment rulemaking procedures. The bioequivalence and RTR regulations do not support Petitioner's arguments, either. The bioequivalence regulations permit study design flexibility, and the RTR regulations do not require that FDA reject, on its face, an ANDA containing a bioequivalence study that was conducted using a protocol other than one the Agency proposed in a guidance document.

Finally, we also dismiss Sigmapharm's statement about the "especially important" consistent application of the Draft RTR Guidance in the case of paragraph IV ANDAs. We agree with Petitioner that FDA's regulations and policies should be consistently applied. However, if Petitioner truly believes this is the case, then the Draft RTR Guidance should be no more or less important to a paragraph IV ANDA than to any other ANDA. Bioequivalence determinations have nothing to do with paragraph IV certifications. This argument is tangential to the real question of whether FDA must refuse to receive an asenapine maleate ANDA containing bioequivalence studies other than those proposed in draft guidance. For all of the reasons stated, the answer is no.

## III. SECOND ARGUMENT: SIGMAPHARM FAILS TO RECOGNIZE THAT THERE ARE MULTIPLE SCIENTIFICALLY-VALID WAYS TO DEMONSTRATE THAT A PROPOSED GENERIC DRUG PRODUCT IS BIOEQUIVALENT TO THE RLD

A. Sigmapharm Ignores the Complexities of Contemporary Drug Development

Sigmapharm asserts that time cannot be used as an appropriate justification for not following FDA's proposals in the Draft BE Guidance. Sigmapharm asserts that, despite the "limited period of time" between issuance of the Draft BE Guidance and the NCE-1 date, it was able to complete the bioequivalence study that FDA first recommended in mid-June 2013.[66] As we address below in Section III.B., there are many ways to design a bioequivalence study based upon valid scientific principles that have nothing to do with the time period available to conduct a study. Nonetheless, Sigmapharm is naïve to believe that the timeframe involved here was

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[65] Winston & Strawn Comments, at 5 ("To the extent a non-binding draft guidance could ever form the basis for the Agency refusing to accept an ANDA, its retroactive application would raise serious questions of procedural fairness.").

[66] Petition, at 5.

adequate to complete the bioequivalence study as proposed by FDA, and its arguments to the contrary are disingenuous.

By arguing that all ANDA sponsors should have been able to design, conduct, and analyze a bioequivalence study in several weeks' time, Sigmapharm glibly ignores the complexities of the ANDA development process. This leads us to consider whether Petitioner had already designed or implemented the recommended bioequivalence study *prior to* FDA's release of the Draft BE Guidance (perhaps for another unrelated bioequivalence study) because, before that document was issued, no asenapine maleate ANDA sponsor would have had reason to believe that FDA would propose bioequivalence studies in patients and not healthy individuals.

The ANDA development process is much more complex than Petitioner acknowledges. Sponsors nearly always conduct pilot studies to facilitate bioequivalence determinations, as such studies can validate analytical methodology, assess variability, or determine appropriate time intervals between sample collections.[67] These pilot studies are an important part of the bioequivalence study protocol design process – a fact not lost on Sigmapharm, as it conducted its own pilot bioequivalence study on asenapine maleate in healthy individuals.

As in the case of any clinical study conducted in humans, certain bioavailability and bioequivalence studies may also be covered by an investigational new drug application ("IND").[68] Even when no IND is required, the study must at minimum be conducted to protect human subjects and be reviewed by an IRB.[69] In the case of an uncomplicated ANDA, an IRB must still review the bioequivalence study to ensure compliance with good clinical practices ("GCPs"). The asenapine maleate Draft BE Guidance requires IRB approval.[70]

Recruiting subjects can be difficult as well. It is not unreasonable to assume that the recruiting period for a bioequivalence study in schizophrenic or bipolar patients could take at least six months. Recruiting investigators with access to the relevant patient population and experience in conducting such studies, as well as retaining patients with these particular diseases, can be difficult. The patient populations are known to have drug treatment compliance problems.[71] Furthermore, dropouts can lead to an insufficiently powered study, resulting in the need to recruit even more patients.

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[67] ANDA BE Guidance, at 3.

[68] 21 C.F.R. § 320.31(a), (b).

[69] 21 C.F.R. § 320.31(d)(2), *citing* 21 C.F.R. Part 50 (protection of human subjects) and Part 56 (IRBs).

[70] Draft BE Guidance, at 2.

[71] Gonzales, Thompson, and Moore, at 333 (stating that the average medication adherence estimate across studies in bipolar disorder is 30-50% and, "[a]s with most chronic illnesses, adherence to medication regimens is a major focus in clinical and research settings.").

Finally, the bioequivalence study must be completed, the samples collected must be assayed by a validated bioanalytical method and then statistically and pharmacokinetically analyzed, and safety data must be medically reviewed and appropriately summarized and presented. All data generated during the drug development process for a drug product formulation proposed for commercial marketing must be analyzed and submitted in the ANDA.[72]

Sigmapharm's Petition ignores the fact that bioequivalence studies require thorough planning and execution, and cannot be completed in a matter of weeks.[73] As a result, we must consider whether Sigmapharm had already designed its protocol in patients and received IRB approval prior to the release of the Draft BE Guidance or had prior information that the guidance was forthcoming and would propose a steady-state study in patients. In the absence of asenapine maleate bioequivalence guidance, any reasonable ANDA sponsor would have consulted the existing bioequivalence regulations and guidance documents, the NDA sponsor's bioavailability and bioequivalence studies (Section III.C, below), and the FDA bioequivalence recommendations for other atypical antipsychotic drug products (Section III.C., below). No sponsor considering these resources before the Draft BE Guidance was issued would have reason to believe that FDA would recommend asenapine maleate studies in patients. Sigmapharm's ignorance of this fact is both naïve and disingenuous.

B. Sigmapharm Ignores Legal Precedent and Scientific Justification for Developing Flexible Bioequivalence Standards

Sigmapharm argues that the asenapine maleate Draft BE Guidance represents "*the established standard*" for determining asenapine maleate bioequivalence. We have already discussed the non-binding nature of draft and final guidance documents, and neither the regulations nor guidance documents support Petitioner's refuse to receive argument. On these bases alone FDA should therefore reject the Petition. This conclusion is further supported by the Petitioner's erroneous argument that there is only one "established standard" for determining bioequivalence for any drug product, including asenapine maleate.

FDA regulations provide study design flexibility to ensure that the most sensitive detection method is chosen to identify a bioequivalence difference between drug products. The regulations state that the selection of a bioequivalence method depends upon several factors, such as the purpose of the study, the analytical methods available, and the drug product at issue.[74] For these reasons, FDA recognizes that there are a variety of means to establish

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[72] 21 C.F.R. § 314.94(a)(7); 21 C.F.R. § 320.21(b)(1).

[73] Winston & Strawn Comments, at 5.

[74] 21 C.F.R. § 320.24(a).

bioequivalence.[75] The goal it to utilize an approach that optimizes the ability to detect bioinequivalence.

For most drugs that are systemically available, FDA recommends a two-period, two-sequence, two-treatment, single-dose, crossover study in healthy adults.[76] As the most sensitive way to detect bioinequivalence, in certain cases a multiple-dose study may be conducted using appropriate administration and sampling to ensure that steady-state is achieved. FDA guidance also acknowledges that bioequivalence studies may use patients whose disease is stabilized in certain circumstances.[77]

There are well-known options to measure bioequivalence or to narrow drug product variability that do not involve a steady-state bioequivalence protocol carried out in patients. For example, the statistical power of the study can be ensured by increasing the number of subjects, as stated in the Draft BE Guidance.[78] Sponsors may also use a reference-scaled average bioequivalence design, another option identified in the Draft BE Guidance.[79] A reference-scaled average bioequivalence study design adjusts the bioequivalence limits by scaling to within-subject variability of the RLD.[80] This approach permits intra-subject variations to be considered during product testing and has supported several FDA approvals of highly-variable generic drugs.[81] The Draft BE Guidance recommends that if an asenapine maleate ANDA sponsor uses a reference-scaled average bioequivalence study design, it should provide evidence of the highly-variable bioequivalence parameters.[82]

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[75] 21 C.F.R. § 320.24(b).

[76] ANDA BE Guidance, at 3-4.

[77] *Id.*, at 4-5.

[78] Draft BE Guidance, at 2.

[79] *Id.*, at 1. FDA refers sponsors to the progesterone capsule draft bioequivalence guidance for further information about this approach. *Id.*

[80] Davit B. and Conner D., *Reference-Scaled Average Bioequivalence Approach*, in Kanfer I. and Shargel L., eds., Generic Drug Product Development – International Regulatory Requirements for Bioequivalence. New York, NY: Informa Healthcare, 2010: 271-272; Davit B. *et al*, *Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration*, THE AAPS JOURNAL 14(4):915-924 (December 2012); Desai J. and Jain P., *Reference Scaled Average Bioequivalence: Scaling Approach for the Highly Variable Drugs*, INTERNATIONAL J. PHARMACEUTICAL RESEARCH AND INNOVATION 4:20-21 (2011).

[81] Davit, at 920-921 (noting that FDA had fully approved four (and tentatively approved one) highly-variable drugs using the reference-scaled average bioequivalence approach).

[82] Draft BE Guidance, at 1.

Finally, the historic 90% confidence interval ("CI") of results that must fall within 80-125% for both area under the curve ("AUC") and maximum concentration ("$C_{max}$") can be narrowed to 90-111.11% (and can be specified to include the 100% or 1.0 point). The FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology discussed this issue with respect to narrow therapeutic index drugs at its April 2010 meeting, and FDA adopted the position for discussion at the July 2011 meeting without Committee vote.[83]

Sigmapharm is legally and factually incorrect to assert that the Draft BE Guidance recommendations are "the established standard" for determining asenapine maleate bioequivalence. The Agency's regulations allow flexible bioequivalence study design to ensure that the most sensitive detection method for establishing bioequivalence is chosen. This approach is supported by several informal interpretive statements. Sponsors are free to deviate from any recommendations that the Agency chooses to issue in non-binding guidance documents.

C. FDA Proposes Bioequivalence Studies in Healthy Individuals for the Majority of Atypical Antipsychotics, Even When there are Known Safety Issues

Many of FDA's bioequivalence recommendations for the other atypical antipsychotic drug products propose using healthy individuals, *even when* there are known safety issues. Although a blanket recommendation about bioequivalence study design across members of a drug class is not appropriate, this observation about other atypical antipsychotics nonetheless negates Sigmapharm's argument the patients should necessarily be used for asenapine maleate bioequivalence studies because of putative safety issues in healthy individuals.

1. *Bioequivalence Recommendations for Other Atypical Antipsychotics*

We reviewed bioequivalence recommendations for sixteen atypical antipsychotic drug product dosage forms, comparing the number and recommended design of the bioequivalence studies (**Attachment A**). In twelve of these sixteen guidance documents (75%), FDA recommended that the studies be conducted in healthy individuals, even though in eight of these twelve documents FDA noted a variety of safety concerns such as life-threatening adverse events, a high rate of syncope and syncope-like events in healthy individuals, and risk of QT prolongation.

In only four of sixteen guidance documents (25%) did FDA recommend bioequivalence studies in patients. In one of these four cases, the Agency recommended two studies in healthy individuals plus one study in patients. In another case, sponsors were advised to conduct one *in vitro* bioequivalence study and one bioequivalence study in patients. Finally, in only two cases

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[83] *See* FDA Advisory Committee for Pharmaceutical Sciences meeting materials, *available at* http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/default.htm.

(including asenapine maleate) did FDA recommend completion of a single study in patients receiving the drug product.

These examples illustrate that FDA has largely proposed conducting bioequivalence studies for the atypical antipsychotic drug products with healthy individuals, not patients, even when FDA acknowledges known safety risks. Considering these facts before the issuance of the Draft BE Guidance, sponsors would have had little reason to believe that the Agency would recommend the use of patients for asenapine maleate bioequivalence studies and not healthy individuals.

2. *The Asenapine Maleate NDA Sponsor Conducted Bioavailability and Bioequivalence Studies in Healthy Individuals*

Significantly, the asenapine maleate NDA sponsor conducted not only absolute and relative bioavailability studies in healthy male subjects, but it conducted bioequivalence studies (due to product formulation changes) in healthy individuals as well. These studies are summarized as follows:

- Absolute bioavailability study (1) – Single sublingual dose in healthy male subjects.[84]
- Absolute bioavailability study (2) – Single dose, two-way crossover design in healthy adult males.[85]
- Relative bioavailability study (1) – Randomized, open-label, placebo-controlled, parallel-design, single-dose, fixed sequence study of drug administered sublingually and in oral solution in two groups of healthy adult males.[86]
- Relative bioavailability study (2) – Three-way, three-period crossover study in healthy males using drug administered via sub-lingual or buccal routes versus the sublingual route.[87]
- Pivotal bioequivalence study (1) – Single-center, open-label, randomized, single-dose, three-treatment, three-crossover study in healthy males and females.[88]
- Pivotal bioequivalence study (2) – Randomized, open-label, single-dose, two-way crossover study in healthy males and females.[89]

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[84] SAPHRIS clinical pharmacology review (May 15, 2008), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022117s000TOC.cfm, at 181-182 of 520.

[85] *Id.*, at 182-184 of 520. The sponsor subsequently combined the results from these two studies to obtain the overall estimate of absolute bioavailability. *Id.*, at 181, 185-186 of 520.

[86] *Id.*, at 187-188 of 520.

[87] *Id.*, at 189-190 of 520.

[88] *Id.*, at 191-194 of 520.

[89] *Id.*, at 195-205 of 520.

- Bioequivalence study – Open-label, randomized, two-way crossover in healthy males.[90]

The NDA sponsor's study designs are significant. FDA clearly permitted that sponsor to use healthy individuals, contradicting Sigmapharm's assertion that only patients should be used because of asenapine maleate safety risks. Moreover, one of the NDA sponsor's pivotal BE studies assessed the observed adverse events, and noted that there were zero withdrawals due to trial emergent signs and symptoms serious adverse events.[91] These observations about the NDA sponsor's studies negate Sigmapharm's safety arguments (see Section III.D., below), and bolster the contention that an ANDA sponsor would be more likely to conduct bioequivalence studies in healthy individuals than in patients.

D. Sigmapharm Confuses the Purpose of Bioequivalence Studies with Drug Safety Issues

Sigmapharm asserts that its pilot bioequivalence study conducted with healthy volunteers led to "an alarmingly frequent occurrence of adverse events" that included bradycardia, extrapyramidal symptoms, and "other events" that caused the individuals to quit the study. The Petitioner states that the Draft BE Guidance, which recommends studying patients, thus "obviated the safety issues that Sigmapharm observed."[92] By linking its observed adverse events with the bioequivalence study design, the Petitioner confuses the role of drug safety and bioequivalence in the ANDA development and approval process and obfuscates the real issue regarding bioequivalence protocol design and receipt of an ANDA.

Bioequivalence studies are used to determine whether there is a significant difference between the RLD and the proposed generic drug in the rate and extent to which the active ingredient becomes available at the site of action.[93] Although safety is of course monitored and reported, bioequivalence studies are not designed to generate a statistically-valid drug safety profile. FDA has addressed the assumption that bioequivalent drug products are equally safe, stating that multiple factors other than bioequivalence affect drug safety and effectiveness, including inactive ingredients, compliance with current good manufacturing practices ("cGMPs"), compendial and other standards, and drug product labeling.[94] Although the safety of any study subject cannot be ignored, bioequivalence and safety are two different drug development objectives.

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[90] *Id.*, at 206 of 520.

[91] *Id.*, at 202 of 520.

[92] Petition, at 5.

[93] 21 C.F.R. § 320.1(e).

[94] 42 Fed. Reg. 1624, 1625 (January 7, 1977).

Sigmapharm cites a 2001 journal article to support its argument that the "requirement" to use patients in asenapine maleate bioequivalence studies is intended to protect participant safety.[95] The article[96] discusses differences in drug tolerability between healthy individuals and patients, citing studies of haloperidol (a typical antipsychotic) and clozapine (an atypical antipsychotic). The article also cites FDA's recommendation that clozapine bioequivalence studies should be conducted in patients, a fact we noted in Attachment A.

This article does not provide the scientific support that the Petitioner believes it does. It does not discuss asenapine maleate, nor does it provide an overview of potential safety or tolerability issues regarding the majority of the atypical or typical antipsychotics. Instead, the article cites only two specific drug products. As a result, it does not demonstrate or even suggest that all atypical antipsychotic bioavailability or bioequivalence studies should be conducted with patients, including asenapine maleate. In fact, the heterogeneity of the atypical antipsychotic drug products as a class has been noted elsewhere.[97] This article, therefore, does not support Sigmapharm's sweeping conclusion that safety issues dictate the bioequivalence study design for asenapine maleate.

Sigmapharm's statement that the Draft BE Guidance "obviated the safety issues" it observed during its pilot bioequivalence study demonstrates that the Petitioner confuses the significance of studies designed to assess safety with studies designed to determine bioequivalence but which might include safety observations. FDA continues to recommend bioequivalence studies in healthy individuals for the majority of the other atypical antipsychotics, even though the Agency recognizes certain associated safety concerns. Therefore, FDA should reject the Petitioner's argument that safety issues trump the flexibility of bioequivalence study design inherent in the regulations.

E. Conclusions

FDA should reject Sigmapharm's Petition because it fails to recognize that bioequivalence study recommendations are not absolute. ANDA development is a complex process, and bioequivalence studies cannot be designed, executed, and redesigned on a moment's notice. Bioequivalence may be demonstrated in multiple different ways, as long as the most accurate, sensitive, and reproducible approach is chosen.

In the absence of asenapine maleate draft guidance – which did not exist prior to mid-June 2013 – a sponsor would have little reason to anticipate that FDA would recommend bioequivalence studies in patients for this drug. The bioequivalence regulations and guidance

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[95] Petition, at 4.

[96] Cutler N., *Pharmacokinetic Studies of Antipsychotics in Healthy Volunteers Versus Patients*, J. CLIN. PSYCHIATRY 62(suppl. 5):10-13 (2001).

[97] Samalin L., Charpeaud T., and Llorca P.-M., *Asenapine in Bipolar I Disorder: Evidence and Place in Patient Management*, THER. ADV. CHRONIC DIS. 4(1):5-14 (2013).

documents state the FDA typically recommends in vivo studies in healthy individuals. Seventy-five percent of bioequivalence recommendations for atypical antipsychotic drug products include healthy individuals, and the asenapine maleate NDA sponsor in fact conducted both bioavailability and bioequivalence studies in healthy individuals. A study demonstrating the bioequivalence of a generic asenapine maleate drug to the RLD does not have to be rejected merely because adverse events may have been observed.

Finally, we note that Petitioner's observation about an "alarmingly frequent occurrence of adverse events" during its pilot bioequivalence study in healthy individuals seems to be an outlier based upon what has been observed by others. Like the NDA sponsor's observations during its pivotal bioequivalence study, our client observed no serious adverse events during bioequivalence studies, and neither did at least one other ANDA sponsor.[98] Sigmapharm's observation causes us to wonder how exactly it conducted its study. Because the Petitioner did not make its bioequivalence study or details about the adverse events available for review with its Petition, Sigmapharm deprives FDA and the public of the opportunity to completely address the underlying basis for its observed adverse events, as discussed immediately below.

## IV. THIRD ARGUMENT: SIGMAPHARM DOES NOT INCLUDE THE FAILED BIOEQUIVALENCE PILOT STUDY PROTOCOLS, PIVOTAL STUDY PROTOCOLS, STUDY REPORTS, AND ADVERSE EVENT DETAILS THAT FORM THE BASIS FOR ITS ARGUMENTS, IN CONTRAVENTION OF FDA REGULATIONS

Sigmapharm relies upon the adverse events it purportedly observed during a pilot bioequivalence study in healthy individuals as the basis for its conclusion that only patients should be used in asenapine maleate bioequivalence studies. As discussed, Sigmapharm's arguments confuse the underlying developmental objectives of safety and bioequivalence studies. Nonetheless, because the Petitioner relies upon its observed adverse events during the pilot bioequivalence study as the basis for its arguments, it must provide the pilot study protocols, pivotal study protocols, study reports, and details about these adverse events with its Petition. Further, by arguing that its pivotal studies in patient subjects served to protect the safety of study subjects better than studies using healthy subjects, Sigmapharm also is making its pivotal studies relevant to its Petition. Therefore, Sigmapharm must also provide the study protocol, study report, and data from its pivotal studies. Sigmapharm has not provided any such data or information to support its safety argument, in clear contravention of FDA's procedural regulations. As a result, the Petitioner has denied FDA, industry, and the public at large the opportunity to fully address the matters giving rise to its arguments.

FDA regulations specify the procedures and requirements for filing a Citizen Petition.[99] FDA will reject a submission for filing if these requirements are not met or, if the submission has

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[98] Winston & Strawn Comments, at 3-4.

[99] 21 C.F.R. §§ 10.20; 10.30(b).

already been filed, the Agency will not consider any portion that fails to comply with the regulations.[100]

Any information "referred to or relied upon in a submission is to be included in full and may not be incorporated by reference."[101] FDA has interpreted this regulatory provision to mean that a Citizen Petition must include all information referred to or relied upon by the petitioner, whether favorable or unfavorable to the petitioner's claims.[102] Furthermore, the Citizen Petition certification requirement also mandates that petitioners must certify that "this petition includes all information and views upon which the petition relies."[103]

Sigmapharm does, in fact, provide a certification in its Petition, even though it knows that it has not included all required information. Sigmapharm provides the Draft BE and Draft RTR Guidances as attachments, but these documents are readily available to the public and are not required to be included.[104] It is the data and information cited in the Petition which is *not* publicly accessible that should have been included.

FDA must reject any argument that Sigmapharm cannot disclose this information because it is confidential as part of an ANDA submission. Petitioner has already publicly divulged the existence of its ANDA, including several key facts about its pilot bioequivalence study. FDA is not required to provide information in an unapproved ANDA to the public, although the Agency may exercise its discretion and disclose a summary of safety and effectiveness data that are "appropriate for public consideration of a specific pending issue."[105] This fact does not relieve Sigmapharm of its duty to make all information on which its Petition relies available to the public for review and comment.

Therefore, given Sigmapharm's failure to meet the Citizen Petition regulatory requirements, FDA should reject that portion of the Petition that relies upon Sigmapharm's safety arguments. Because the entire Petition in fact rests upon the assertion that asenapine

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[100] 21 C.F.R. § 10.20(c)(6).

[101] 21 C.F.R. § 10.20(c).

[102] FDA, "Guidance for Industry: Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act" (June 2011), *available* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf, at 5. FDA does, however, have discretion to consider information in addition to what has been provided in the docket. *See, e.g.,* Tummino v. Hamburg, 936 F. Supp. 2d 162, 194 (E.D.N.Y. 2013).

[103] 21 C.F.R. § 10.30(b). For Citizen Petitions subject to FFDCA § 505(q), the required certification also addresses including "all information and views upon which the petition relies." FFDCA § 505(q)(1)(H), *codified at* 21 U.S.C. § 355(q)(1)(H).

[104] 21 C.F.R. § 10.20(c)(1)(iii).

[105] 21 C.F.R. § 314.430(d)(1).

maleate bioequivalence studies cannot be conducted in healthy individuals because of safety concerns, FDA should reject the entire Petition. In the alternative, if FDA decides not to reject a portion or all of the Petition, and Sigmapharm elects not to withdraw the same, then it must be required to produce all such information regarding its pilot and pivotal studies.

## V. CONCLUSIONS

For all of the reasons explained in this submission, FDA should deny Sigmapharm's Citizen Petition on the following three bases:

(1) Sigmapharm erroneously relies upon draft guidance as legally binding;

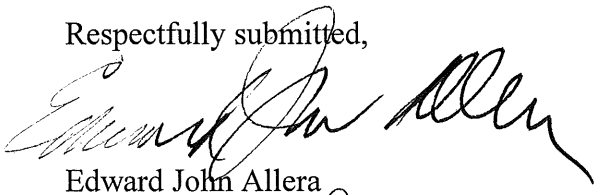
(2) Sigmapharm fails to recognize that there are multiple scientifically-valid ways to demonstrate that a proposed generic drug product is bioequivalent to the RLD; and

(3) Sigmapharm does not include the failed bioequivalence pilot study protocols, pivotal study protocols, study reports, and adverse events details that form the basis for its arguments, in contravention of FDA regulations.

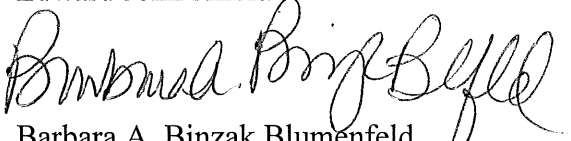
## VI. CERTIFICATION

I certify that, to my best knowledge and belief: (1) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about December 13, 2013. 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: Breckenridge Pharmaceutical, Inc. 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,



Edward John Allera



Barbara A. Binzak Blumenfeld

Tina Hu-Rodgers

Enclosure: Attachment A

cc (via electronic mail only):

Kathleen Uhl, M.D.
Acting Director, Office of Generic Drugs

Elizabeth Dickinson, J.D.
Chief Counsel, Office of the Chief Counsel