DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

MAY 8 2014

Rakesh Grover
President & Chief Operating Officer
Sigmapharm Laboratories, LLC
3375 Progress Drive
Bensalem, PA 19120

Re: Docket No. FDA-2013-P-1623

Dear Mr. Grover:

This letter responds to your citizen petition, which was received by the Food and Drug Administration (FDA or Agency) on December 9, 2013 (Petition).[1] The Petition requests that FDA refuse to receive any abbreviated new drug application (ANDA) for SAPHRIS (asenapine maleate) that does not include the results of a bioequivalence study performed in accordance with FDA's June 24, 2013 product-specific draft bioequivalence guidance (June 24 Draft BE Guidance) for asenapine maleate (Petition at 1).[2] The Petition also requests that FDA consider the date that an ANDA first contained the results of a bioequivalence study performed in accordance with this draft guidance to be the filing acceptance date for purposes of determining the ANDA's eligibility for 180-day exclusivity (Petition at 1).

FDA has carefully considered the information submitted in your petition and other relevant information available to the Agency, including the comments to your petition submitted by Buchanan Ingersoll & Rooney PC and Winston & Strawn LLP.[3] Based on our review of these materials and for the reasons described below, the Petition is denied.

[1] The Sigmapharm Laboratories, LLC (Sigmapharm) petition was submitted twice previously with deficient 505(q)(1)(H) certifications. These petitions, which were docketed as FDA-P-2013-1399 and FDA-2013-P-1554, were each subsequently withdrawn.

[2] The notice of availability of this draft guidance was published in the *Federal Register* on June 20, 2013 ("Draft and Revised Draft Guidances for Industry Describing Product-Specific Bioequivalence Recommendations; Availability," 78 FR 37230 (June 20, 2013)). The June 24 Draft BE Guidance and other guidances referenced in this response are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[3] Buchanan Ingersoll & Rooney PC's comment was submitted on February 25, 2014; Winston & Strawn LLC's comment was submitted on March 4, 2014. These comments are available at http://www.regulations.gov. Both were submitted twice previously with either deficient or absent 505(q)(1)(I) verifications.

I. BACKGROUND

A. SAPHRIS

SAPHRIS (asenapine maleate) (new drug application (NDA) 22-117) was approved by FDA on August 13, 2009. It is an atypical antipsychotic indicated for (1) the treatment of schizophrenia and (2) the acute treatment of manic or mixed episodes associated with bipolar I disorder (either as monotherapy or as adjunctive therapy with lithium or valproate). There are currently no approved generic versions of SAPHRIS, which is subject to 5-year New Chemical Entity (NCE) exclusivity set to expire on August 13, 2014. Organon USA Inc., the NDA holder for SAPHRIS, has listed two patents for this product in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly referred to as the Orange Book), which expire in 2020 and 2026.

B. Legal and Regulatory Framework

1. ANDA Approval

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)), which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective.

To rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the FD&C Act). In addition, an ANDA must contain, with certain exceptions not relevant here, information to show that the proposed drug has the same active ingredient(s), indications for use, route of administration, dosage form, strength, and labeling as the RLD (section 505(j)(2)(A) of the FD&C Act). FDA must approve an ANDA unless the information submitted in the ANDA is insufficient to meet the requirements delineated in section 505(j)(2)(A), including a demonstration of bioequivalence (section 505(j)(4) of the FD&C Act).

The basic assumption underlying the Hatch-Waxman Amendments is that bioequivalent drug products that meet the requirements for ANDAs under section 505 of the FD&C Act are therapeutically equivalent and may be substituted for each other.

2. Demonstrating Bioequivalence

The purpose of demonstrating bioequivalence to the RLD is to determine whether changes in the formulation or manufacturing of the proposed product affect the rate at or extent to which the active ingredient reaches the primary site of action. FDA regulations (at 21 CFR part 320) list acceptable methodologies for determining the bioequivalence

of drug products, which include pharmacokinetic studies, pharmacodynamic studies, comparative clinical trials, and in vitro studies. The selection of the method used depends on the purpose of the study, the analytical methods available, and the characteristics of the drug product under consideration. Applicants are required to conduct bioequivalence testing using the most accurate, sensitive, and reproducible approach available (21 CFR 320.24). The courts have made clear that FDA has discretion under the FD&C Act to determine the appropriate means of demonstrating bioequivalence for a given drug (see, e.g., *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 19 (D.D.C. 2009), *Somerset Pharms. v. Shalala*, 973 F. Supp. 443, 453 (D. Del. 1997)).

FDA's general recommendation for demonstrating bioequivalence of systemically acting products with in vivo data is administration of single-doses of the test and reference drug products to healthy subjects, with measurement of the concentrations of the test and reference drugs in blood, plasma, or serum over time.[4] FDA's position that single-dose studies should generally be used is based on the fact that these studies "are *generally* more sensitive in assessing release of the drug substance from the drug product into the systemic circulation" (General BE Guidance at 8) (emphasis in original).[5] As FDA regulations and guidance recognize, in some circumstances, steady-state bioequivalence studies may be more appropriate for a particular product,[6] including when safety considerations suggest using patients who are already receiving the medication.[7]

To evaluate the rate and extent of test drug absorption, the measured drug concentrations for each subject should be plotted against time of measurement with the sampling time on the horizontal (x) axis and corresponding drug concentration on the vertical (y) axis. The relevant pharmacokinetic parameters calculated from these data include the area under the concentration-time curve (AUC), maximum or peak drug concentration (C_{max}), and the time required to reach the peak drug concentration after administration (T_{max}).

FDA considers products bioequivalent when the 90 percent confidence intervals for test/reference pharmacokinetic parameters (AUC and C_{max})[8] are entirely within an 80 to 125 percent acceptance interval.[9] The choice of the 80 to 125 percent acceptance

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[4] See 21 CFR 320.26(a)(1) ("an in vivo…bioequivalence study should be a single-dose comparison of the drug product to be tested and the appropriate reference material conducted in normal adults"); FDA draft guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (Draft ANDA BA/BE Guidance) at 8 (December 2013); FDA guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (General BE Guidance) at 8 (March 2003).

[5] See also Draft ANDA BA/BE Guidance at 5.

[6] See, e.g., 21 CFR 320.27(a); General BE Guidance at 8.

[7] Draft ANDA BA/BE Guidance at 5.

[8] FDA also conducts a qualitative review of test/reference bioequivalence for the entire pharmacokinetic profile, including T_{max}. In some circumstances, FDA requires application of a confidence interval to additional pharmacokinetic parameters (such as partial AUC).

[9] See FDA guidance for industry on *Statistical Approaches to Establishing Bioequivalence* (January 2001). For narrow therapeutic range drug products, FDA has stated that the traditional BE limit of 80 to 125 percent for non-narrow therapeutic range drugs should apply unless indicated otherwise by specific guidance (General BE Guidance at 20).

interval reflects decades of scientific data on the variability of product characteristics within and between batches, as well as the biological variability in patients. From these data, FDA concluded that the variability in pharmacokinetic values allowed under this acceptance interval would not adversely affect clinical outcomes because the variability was within the range of differences that can arise from other product-specific and biological factors.[10]

3. Bioequivalence Recommendations for Asenapine Maleate

In product-specific, draft bioequivalence guidance for asenapine maleate posted on June 24, 2013, FDA recommended use of steady-state bioequivalence studies in patients who have been taking a stable dose of asenapine maleate for at least 3 months, rather than single-dose studies in healthy patients. This recommendation was motivated by safety concerns associated with the dosing of healthy subjects on asenapine maleate, given the significant adverse events observed with use of asenapine maleate (including hypotension, bradycardia, tachycardia, and sinus pause).

4. New Chemical Entity and 180-Day Exclusivity

A 5-year period of NCE exclusivity is granted to certain eligible NDAs for products containing chemical entities never previously approved by FDA (section 505(j)(5)(F)(ii) of the FD&C Act). ANDAs referencing products that are the subject of 5-year NCE exclusivity may not be submitted until expiration of the 5-year exclusivity period (id.), with one exception. ANDAs that contain what is commonly referred to as a "paragraph IV" certification that a patent listed in the Orange Book for the RLD is invalid or will not be infringed by the proposed generic product may be submitted 1 year prior to expiration of the 5-year period (id.). This date is commonly referred to as the "*NCE-1 date*."

An ANDA applicant submitting a paragraph IV certification must provide the NDA holder and the patent owner notice of its patent certification, including a description of the legal and factual basis for its assertion that the patent is invalid or not infringed (section 505(j)(2)(B) of the FD&C Act). In the case of a patent for which information was submitted to FDA before the date on which the ANDA is submitted, if the NDA holder or patent owner initiates a patent infringement action against the ANDA applicant within 45 days of receiving the required notice, approval of the ANDA generally will be stayed for 30 months from the date of receipt of the notice or such shorter or longer time as the court might order (section 505(j)(5)(B)(iii) of the FD&C Act).

The FD&C Act's 180-day exclusivity provisions give the first applicant(s) to submit an ANDA containing a paragraph IV certification (and thus undertake the risk of patent litigation with the RLD holder) an incentive and reward in the form of the opportunity to be the only ANDA applicant(s) to compete with the innovator for a 180-day period. The FD&C Act defines a "first applicant" as "an applicant that, on the first day on which a

[10] Dighe SV, and WP Adams, 1991, Bioequivalence: A United States Regulatory Perspective. In: PG Welling, LS Tse, and S Dighe, eds., Pharmaceutical Bioequivalence, Marcel Dekker, Inc., New York, 347-380.

substantially complete application containing a [paragraph IV certification] is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a [paragraph IV certification] for the drug" (section 505(j)(5)(B)(iv)(II)(bb)).

5. ANDA Filing Requirements

A substantially complete ANDA is one that is sufficiently complete on its face to permit a substantive review, and includes all the information required by section 505(j)(2)(A) of the FD&C Act.[11] If FDA determines that an ANDA is not sufficiently complete on its face to permit a substantive review, it will refuse to receive (RTR) the ANDA. FDA regulations at 21 CFR 314.101(d) set out the bases on which FDA may refuse to receive an ANDA, including where the application does not on its face contain information required under section 505(j) (such as a bioequivalence demonstration). FDA recently issued draft guidance for industry on the standards it uses in evaluating the completeness of submitted ANDAs.[12] The Draft RTR Guidance states that submission of a non-recommended in vivo bioequivalence study without adequate justification will result in FDA refusing to receive the ANDA (Draft RTR Guidance at 18).

C. Sigmapharm Petition

Sigmapharm states that it began development activities for its asenapine maleate ANDA with the goal of submitting an application on August 13, 2013, the NCE-1 date for SAPHRIS. As part of these activities, Sigmapharm conducted initial pilot bioequivalence studies in which single doses of the test product were administered to healthy volunteers (Petition at 5). Sigmapharm represents that it terminated its pilot studies, however, after a "very substantial" percentage of enrolled subjects dropped out due to adverse events, including bradycardia and extrapyramidal symptoms (Petition at 5).

Sigmapharm contends that FDA's issuance of the June 24 Draft BE Guidance obviated the safety issues the company had observed in its pilot study by requiring conduct of a study in patients who have been stabilized on the drug, rather than in healthy subjects (Petition at 5). While the time between the issuance of the June 24 Draft BE Guidance and the NCE-1 date for SAPHRIS "was arguably very tight," Sigmapharm claims, it was nevertheless able to perform a new study in time to submit the results as part of its ANDA on the NCE-1 date (Petition at 5-6).

Sigmapharm therefore requests that FDA refuse to receive any ANDA for asenapine maleate that does not similarly include the results of a bioequivalence study performed in accordance with the June 24 Draft BE Guidance (Petition at 1). The Petition asks FDA to consider the date that an ANDA first contained the results of a bioequivalence study performed in accordance with the recommendations in the June 24 Draft BE

[11] Section 505(j)(5)(B)(iv)(II)(cc) of the FD&C Act.
[12] Guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards* (issued October 2013) (Draft RTR Guidance).

Guidance to be the filing acceptance date for purposes of determining the ANDA's eligibility for 180-day exclusivity (id.).

In support of these requests, Sigmapharm argues that FDA must apply consistent standards during the filing review process, particularly where the ANDAs at issue could be "first filed" applications (Petition at 5). Sigmapharm contends that the June 24 Draft BE Guidance is the established standard for demonstrating bioequivalence for asenapine maleate, and that it was possible for other ANDA applicants to conduct new bioequivalence studies in patients after the June 24 Draft BE Guidance was issued (Petition at 6).

Sigmapharm points to the statement in FDA's Draft RTR Guidance that submission of a non-recommended in vivo bioequivalence study without adequate justification will result in an RTR action and argues that the "arguably very tight" period of time between the release of the June 24 Draft BE Guidance and the NCE-1 date should not constitute "appropriate justification" for accepting ANDAs that contain "non-complying studies" (Petition at 5-6). Sigmapharm maintains that FDA's recommendation that patients be used in asenapine maleate bioequivalence testing was intended not just to protect study subjects, but also to ensure the accuracy and reliability of information supporting FDA's bioequivalence determination (given the high drop-out rate expected in healthy subject studies) (Petition at 4-6). Sigmapharm therefore urges FDA to refuse to receive any ANDA that does not include a bioequivalence study that is consistent with the recommendations in the June 24 Draft BE Guidance, and to calculate eligibility for 180 day exclusivity on the basis of the date that an ANDA first contained such a study (Petition at 1).

II. DISCUSSION

The June 24 Draft BE Guidance states that ANDA applicants may use an alternative bioequivalence approach if the approach satisfies the requirements of applicable statutes and regulations. For the reasons described below, if an ANDA applicant conducted acceptable single-dose bioequivalence testing for asenapine maleate in healthy subjects prior to the posting of the June 24 Draft BE Guidance, FDA will not expect the applicant to conduct additional, steady-state bioequivalence testing in patients.[13]

First, for asenapine maleate, single-dose studies in healthy subjects are expected to be (at least) as sensitive in demonstrating bioequivalence as the steady-state patient studies recommended in FDA's June 24 Draft BE Guidance. As described above, FDA's recommendation that bioequivalence testing for asenapine maleate be conducted in patients was made because of safety concerns about dosing healthy subjects, given the significant adverse events associated with asenapine maleate use. This recommendation was not motivated by any expectation that steady-state patient studies would be more accurate or sensitive in demonstrating bioequivalence.

[13] We note that FDA's recently issued Draft RTR Guidance states that submission of a non-recommended bioequivalence study is not grounds for an RTR action where adequate justification exists. As explained below, adequate justification exists here.

Further, FDA's bioequivalence criteria already account for the impact that study dropouts have on the accuracy of the resulting bioequivalence demonstration. Bioequivalence results are calculated on the basis of the number of subjects that complete a bioequivalence study: accordingly, each time a study subject drops out, that person must be removed from the statistical analysis supporting the bioequivalence demonstration. If there are too many dropouts from a study, the confidence interval for the study will become too wide, and bioequivalence criteria will not be satisfied. Were a high number of subjects to drop out of a bioequivalence study for asenapine maleate due to adverse events (as Sigmapharm contends happened in its pilot studies), it is unlikely that the resulting study would satisfy FDA's confidence interval criteria for demonstrating bioequivalence. Sigmapharm's concerns about the accuracy of bioequivalence data resulting from healthy subject studies (Petition at 4) are therefore misplaced.

Finally, given the short window between the issuance of the June 24 Draft BE Guidance and the NCE-1 date for SAPHRIS, ANDA applicants planning to submit applications on the NCE-1 date may reasonably have conducted bioequivalence testing prior to the issuance of this draft guidance, when the existing FDA guidance for asenapine maleate was FDA's general bioequivalence guidance for systemically available drug products – i.e., use of a single-dose study in healthy subjects.[14] Expecting such ANDA applicants to conduct new studies after the June 24 Draft BE Guidance was posted – even though their studies already provide sufficient evidence of bioequivalence – would raise concerns about unnecessary human research. With respect to Sigmapharm's argument (Petition at 5) that FDA must apply "consistent" standards during the filing review process, we note that FDA has discretion to accept different demonstrations of bioequivalence from different applicants referencing the same RLD.[15]

As a result, if a successful, single-dose, healthy subject study that meets the requirements of the FD&C Act and applicable regulations was conducted prior to the posting of the June 24 Draft BE Guidance, FDA will not refuse to receive an ANDA that includes the results of this study rather than the results of a steady-state bioequivalence study performed in patients. Failure to include the results of a steady-state patient study in such circumstances will therefore not disqualify an ANDA from eligibility for 180-day exclusivity.

[14] See General BE Guidance at 8.

[15] See FDA's Nov. 13, 2012, response to citizen petition submitted on behalf of Jazz Pharmaceuticals (FDA-2012-P-0499) at 13 (available at http://www.regulations.gov); see also *ViroPharma v. Hamburg*, 898 F. Supp. 2d 1, 24 (D.D.C 2012) ("The FFDCA and a number of the FDA's own regulations grant the agency wide discretion in determining whether bioequivalence has been established." (internal quotations and citations omitted)).

III. CONCLUSION

For the reasons discussed above, the Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research