DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 51,641

Tracie A. Buranicz, Pharm.D.
Regulatory Affairs Manager
Organon Pharmaceuticals USA Inc.
56 Livingston Avenue
Roseland, NJ 07068

Dear Dr. Buranicz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Org 5222.

We also refer to the 2nd End of Phase 2 meeting between representatives of your firm and the FDA on April 27, 2004.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

Organon/Pfizer FDA Meeting
Asenapine/Org 5222 (IND 51,641) Second End of Phase II Meeting
April 27, 2004

Organon/Pfizer Participants

Larry Alphs, M.D., Ph.D.	Clinical Development, Pfizer
Mark Ammann, PharmD	Regulatory Affairs, Pfizer
Ana Arango Bossard	Regulatory Affairs, Organon
Howard Berkeley, Ph.D.,	Regulatory Affairs, Organon
Kevin Chartier, Ph.D.	Statistics, Pfizer
Peter Machado, M.Phil.	Regulatory Affairs, Pfizer
Steven Nettler	Principal Statistician, Organon
John Panagides, Ph.D.	Clinical Development, Organon
Stephen Sasson, Ph.D.	Project Team Leader, Pfizer
Peter Schot, Ph.D.	Project Team Leader, Organon

FDA Participants

Russell Katz, M.D.	Director, DNDP
Thomas Laughren, M.D.	Psychopharmacology Team Leader, DNDP
Robert Levin, M.D.	Medical Officer, DNDP
Capt. Steven Hardeman	Senior Regulatory Project Manager, DNDP

[Note: These minutes were prepared by the sponsor. While we are in substantial agreement on their characterization of the meeting, I have added a few comments in brackets to clarify several issues.—T. Laughren.]

Capt. Hardeman welcomed the participants to the meeting, followed by a brief introduction by all the participants. The following is the list of the questions and a summary of the discussion for each question.

QUESTIONS RELATED TO SCHIZOPHRENIA INDICATION: NEGATIVE SYMPTOMS

Dr. Ammann presented a summary of the issues pertaining to the first question (negative symptoms) and asked for the Agency's feedback.

Question 1.1.1: Does the Agency agree that the proposed negative symptom studies (041-003 and 25538), using olanzapine as an active control, address concerns regarding study design and are adequate to obtain labelled indication for the efficacy of asenapine in the treatment of negative symptoms of schizophrenia?

Discussion: Dr. Katz and Dr. Laughren stated that they agree negative symptoms is a reasonable target, but that the methodology for evaluating this domain is "immature." Specifically, they stated that there are a number of issues related to the development of negative symptoms that would confound the interpretation of the results. These include the following:

- **Presently there is no consensus in the scientific community on the definition of negative symptoms.**

- Changes in negative symptoms must be differentiated from changes in cognitive symptoms. Dr. Laughren mentioned that cognition and negative symptoms "track together in longitudinal studies."
- Changes in negative symptoms must be differentiated from changes in positive symptoms.
- The Agency stated that negative symptoms of schizophrenia, in some cases, may simply be an adverse effect of medications used to treat the disorder. In this case, a benefit in negative symptoms demonstrated by an investigational agent might simply reflect a better side-effect profile. While this benefit in the side-effect profile might be worthy of recognition in its own right, a different claim (i.e. efficacy for negative symptoms) would require resolution of this confounding factor.

In response, Organon/Pfizer agreed that, although a precise definition of negative symptoms has not been agreed upon by the field of psychiatry, there is general consensus that this is a domain of symptoms that is distinct from other symptom domains of schizophrenia (e.g. positive symptoms, etc.). They further indicated that there is general agreement that this symptom domain represents significant morbidity associated with schizophrenia and is worthy of improved treatment alternatives. Organon/Pfizer recognized that there are a number of important potential confounds in interpreting these analyses, but it was agreed that with the right patient selection, design and analysis a meaningful interpretation of effects relative to negative symptoms was possible and, if these issues were adequately addressed an indication for the treatment of negative symptoms of schizophrenia was possible.

Regarding the proposed studies, the issues raised by the Agency included the following:

- To obtain an indication for the treatment of negative symptoms of schizophrenia, the sponsor must demonstrate a statistical and clinically significant change in the primary outcome endpoint(s) with asenapine treatment. An improvement in the scale in relation to the control must be clear, along with the assurance that the change seen is clinically relevant to the patient. To confirm this, a co-primary endpoint must be identified and demonstrate a functional or otherwise clinically meaningful benefit. The Agency stated that CGI-NS would not be an acceptable co-primary endpoint because it is redundant to the Negative Symptom Assessment (NSA). It was agreed that alternative endpoints to demonstrate clinical relevance of changes identified on the NSA would be explored and a proposal would be presented to the FDA at a later date.
- It was agreed that the entry criteria should identify an appropriate, affected population. These criteria should address symptoms that may confound interpretation of the drug effect.
- Regarding concerns as to whether patients who are randomized to the comparator arm are being appropriately dosed, the following agreement was reached:
  - The Agency acknowledges that it would be extremely difficult to employ placebo as a control in this population, because of the possibility of patient relapse and confounds that would occur from the potential exacerbation of positive symptoms of schizophrenia.
  - In the absence of placebo, they agreed that we would need to demonstrate superiority versus an active control.
  - Efforts should be made to hold other symptoms of schizophrenia (like positive symptoms) constant, so as reduce confounds in interpretation of clinical change seen with treatment.
- Regarding the duration of the proposed studies, both Dr. Katz and Dr. Laughren indicated that schizophrenia is a chronic disorder and negative symptoms persist long term, therefore, a product should demonstrate an enduring benefit, so the recommended duration for these studies is six months. The sponsor indicated some concern about potential drop-out rate of schizophrenia patients in a study of six-month duration. As a result, other designs were suggested, such as evaluations for endpoint analysis when a threshold of 70% of randomized patients remained in a 6-month study. Concern was raised about whether the

sponsor would be committed to high retention with such a design. The Agency indicated that given the stability of this patient population, coupled with the study being active-controlled it should be possible to retain patients in the studies.

- The issue of labeling was raised and although the Agency is willing to consider an indication or other claims for negative symptoms, it would not commit as to where in the labeling the information would appear (i.e., indication section, clinical trial section or even in the adverse event section). The Agency indicated that any wording would be contingent on the results presented from these studies and their interpretation.

Question 1.1.2: Does the Agency agree that stability of negative symptoms of schizophrenia at study entry are adequately demonstrated using a 6-month retrospective history and 1-month prospective evaluation of stability?

Discussion: The Agency indicated that a historical six month stability along with a one month prospective stability period is acceptable.

Question: 1.1.3: Does the Agency agree that the scales to be used in these studies are acceptable for demonstrating improvement in negative symptoms?

Discussion: The Agency stated that they are not familiar with the NSA, but from the information provided it seemed to be measuring the right parameters and should be acceptable. Organon/Pfizer is to provide the Agency with further information pertaining to validity, reliability and interpretation of the NSA.

Question 1.1.4: Does the Agency agree that, to establish differences in efficacy for negative symptoms, asenapine and olanzepine may be flexibly dosed on clinician judgment?

Discussion: There was no concern cited about flexible dosing per se. However, the Agency reiterated the need to ensure that the comparison of the two drugs, in relation to dosing, is fair.

[Note: While we acknowledged the difficulty in conducting a long-term placebo-controlled trial in this population, we also emphasized the difficulty in interpreting an active-control trial, even one showing superiority of the newer drug. Such an outcome would have several different possible interpretations, only one of which would be that the superior drug actually represents a treatment for negative symptoms. A less sanguine interpretation would be that, while both drugs induce negative symptoms, the newer drug is superior with regard to this particular adverse effect.--TPL]

Questions Related to Schizophrenia Indication: Maintenance

Question 1.2: At the EOPII meeting in November 2002, long-term, active controlled studies and a placebo-controlled relapse prevention study were proposed as sources of long-term data to support a labelled claim for maintenance of effect in schizophrenia. After reviewing this program with external experts, it is Organon's and Pfizer's position that the design of the proposed extension studies (i.e., without a placebo arm) can adequately produce the data necessary for establishing an indication for maintenance without reliance on a placebo-controlled relapse prevention trial. Does the Agency agree that the design of these extension studies will support an indication for maintenance of effect in the treatment of schizophrenia?

Discussion: Dr. Katz indicated that the proposed studies violate two principles of trial design that confound interpretation: not comparing randomized groups and not demonstrating superiority to a control.

In response, the sponsor asked some follow-up questions regarding the design of a relapse prevention trial. The first question was whether a three-month retrospective and a one-month prospective stabilization period would be acceptable. Dr. Laughren and Dr. Katz stated that a one-month prospective stabilization would not provide sufficient data for adequate interpretation. Both recommended that the study be conducted with a six-month prospective stabilization period on the investgational drug. While they acknowledged that this recommendation deviates from historical precedence, they indicated that their policy on this issue has been evolving but that this advice is consistent with what they have been telling other sponsors recently. Dr. Alphs asked whether the Agency would be willing to consider an alternative stabilization period. Dr. Katz responded by stating that the Agency would be willing to evaluate and consider an alternative proposal with a reasonable stabilization period if Organon/Pfizer provided a strong justification.

The second question was whether it would be acceptable for the entire relapse prevention study to be conducted in India. Both Dr. Katz and Dr. Laughren acknowledged that it would not be possible to conduct the study in the US. It was noted that although experience with India is limited, they would not preclude conducting the study there as long as the acute studies have a geographically diverse population.

Question Related to Bipolar Indication: Adjunctive Therapy

Question 1.3.1: Does the Agency agree that a study comparing asenapine treatment with placebo as adjunctive treatment to lithium or valproic acid in bipolar I disorder patients experiencing acute manic episodes is adequate for an additional labeling claim for adjunctive therapy for asenapine?

Discussion: The Agency stated that the proposal appears acceptable.

Question Related to Both Indications: Pediatric Studies:

Question 1.4.1: Does the Agency agree that the proposed Organon and Pfizer pediatric plan is compliant with the Pediatric Rule?

Discussion: The Agency indicated that the proposal, with the deferral, was acceptable as long as the efficacy studies are conducted in two separate patient populations: schizophrenia and bipolar I disorder. Organon and Pfizer confirmed that separate studies would be conducted. For the proposed pharmacokinetic study a mixed population would be acceptable.

Question Related to Management of Missing Data:

Question 1.5.1: Would the Agency be willing to consider alternative methods for handling missing data that would be acceptable in place of the traditional Last Observation Carried Forward (LOCF) analysis?

Discussion: Dr. Katz indicated that Organon/Pfizer need to provide proposals for the Agency to comment.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
8/13/04 03:08:23 PM

ACTION PACKAGE CHECKLIST

APPLICATION[1]		
NDA # 22-117 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Saphris Established/Proper Name: asenapine Dosage Form: Sublingual Tablets		Applicant: Organon USA Inc. Agent for Applicant (if applicable):
RPM: Keith Kiedrow		Division: Division of Psychiatry Products

NDAs:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ If no listed drug, check here and explain:

Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.

☐ No changes ☐ Updated
Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

◆ User Fee Goal Date Action Goal Date (if different)	August 13, 2009
◆ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR – January 13, 2009
◆ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

[1] The Application Information section is (only) a checklist. The Contents of Action Package section (beginning on page 3) lists the documents to be included in the Action Package.

Application[2] Characteristics	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): 1 ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	12/10/2008
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other: information advisory

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then e questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

◆ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	N/A
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	N/A
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	N/A
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
◆ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	N/A
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	N/A
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).*	N/A

• **[505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.** **Answer the following questions for each paragraph IV certification:** **(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?** **(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).** ***If "Yes," skip to question (4) below. If "No," continue with question (2).*** **(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?** ***If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*** ***If "No," continue with question (3).*** **(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?** **(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).** ***If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*** **(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?** ***If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*** ***If "No," continue with question (5).***	**N/A**

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (***Summary Reviews***).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	
◆ Copy of this Action Package Checklist[3]	Yes
◆ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
◆ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP, August 13, 2009 In CR package - CR, January 13, 2009
◆ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Identical to label agreed upon with sponsor and included with the AP letter
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	No
• Original applicant-proposed labeling	Yes, from 2/13/09 resubmission And in CR package - August 30, 2007 initial submission version.
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	No
◆ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	

[3] Fill in blanks with dates of reviews, letters, etc.

	[redacted]
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (full color carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	[redacted]
• Most-recent division proposal for (only if generated after latest applicant submission)	N/A
• Most recent applicant-proposed labeling	No
❖ Labeling reviews *(indicate dates of reviews and meetings)*	Contained in various discipline reviews and OSE/SEALD reviews 2/6/2009 7/30/2009 7/6/2009 In CR package – 5/6/2008 5/9/2008 6/2/2008 6/16/2008 10/20/2008
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	DMEPA review 7/30/2009 AP Letter 8/13/2009
[redacted]	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	No
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ August 3, 2009
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	[redacted]
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ August 3, 2009
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	Yes

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Outgoing communications *(if located elsewhere in package, state where located)*	Submission from sponsor with document July 15, 2009
• Incoming submissions/communications	See above
❖ Postmarketing Commitment (PMC) Studies	Yes
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	Grouped with PMR documents
• Incoming submission documenting commitment	Grouped with PMR documents
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	email of 12/12/08 included
• Pre-Approval Safety Conference *(indicate date; approvals only)*	8/07/2009
• Regulatory Briefing *(indicate date)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	Meeting minutes included – 8/3/2004 7/26/2006 3/6/2007 7/28/2005
• EOP2 meeting *(indicate date)*	See above
• Other (e.g., EOP2a, CMC pilot programs)	See above
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	7/30/09
• 48-hour alert or minutes, if available	Not available
	E
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None August 13, 2009
Division Director Summary Review *(indicate date for each review)*	July 31, 2009 In CR package – August 1, 2008 October 15, 2008
Cross-Discipline Team Leader Review *(indicate date for each review)*	July 28, 2009 In CR package - June 12, 2008 May 14, 2008
	F
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	Same as CDTL reviews above
• Clinical review(s) *(indicate date for each review)*	In CR package – June 27, 2008 May 15, 2008 May 1, 2008
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	In CDTL review July 28, 2009

[5] Filing reviews should be filed with the discipline reviews.

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	In CR package - May 1, 2008 clinical review
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	Maternal Health Team Review 7-7-2009 In CR Package - QT Interdisciplinary Review Team April 23, 2008 February 29, 2008
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ Not needed In CR package - 5/13/2008
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	In CR package – 4/7/2008 4/11/2008 6/4/2008 12/17/2008 12/13/2008 1/2/2009
Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	In CR package – April 18, 2008 April 17, 2008
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	In CR package – June 20, 2008 June 30, 2008
Clinical Pharmacology review(s) *(indicate date for each review)*	September 30, 2008 In CR package – June 30, 2008 June 18, 2008 May 20, 2008 May 15, 2008
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	8/7/2009 In CR Package –

G

H

	6/23/2008
• Supervisory Review(s) *(indicate date for each review)*	July 27, 2009 In CR package – June 24, 2008
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	7/27/2009 In CR package – 4/30/2008
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	5/27/2009 In CR package – 1/11/2008 4/8/2008
❖ ECAC/CAC report/memo of meeting	3/30/2009 In CR package – 3/31/2008 6/16/2008
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	7/17/2009 In CR package – 5/23/2008
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• CMC/product quality review(s) *(indicate date for each review)*	3/5/2009 In CR package – 4/11/2008 5/21/2008 6/20/2008
• BLAs only: Facility information review(s) *(indicate dates)*	N/A
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See CMC reviews
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Methods Validation	☒ Completed (per CMC review) ☐ Requested ☐ Not yet requested ☐ Not needed
❖ Facilities Review/Inspection	

• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: see CMC reviews ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	N/A

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) And no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) And all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Organon USA Inc.	07/15/2009
TELEPHONE NO. (Include Area Code) (908) 740-2719	**FACSIMILE (FAX) Number (Include Area Code)** 908-740-4769
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 56 Livingston Ave. Roseland, NJ 07068	**AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE** Organon USA Inc. 56 Livingston Avenue Roseland, NJ 07068 (T) 908-740-2719, (F) 908-740-4769

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*: 22-117

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)	PROPRIETARY NAME (trade name) IF ANY
Asenapine maleate	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)
trans-5-chloro-2,3,3a, 12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7] oxepino [4,5-c]pyrrole(Z)-2-butenedioate(1:1)	Org 5222

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
fast dissolving sublingual tablets	5mg, 10mg	oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of schizophrenia; treatment of acute manic or mixed episodes associated with Bipolar I Disorder

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (NDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION (check one) ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO APPENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
UPDATED: POST APPROVAL REQUIREMENTS & COMMITMENTS

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing class and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and BLAs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
for Tracie Carey	Tracie A. Carey, Pharm.D., Senior Manager & Liaison, Global Regulatory Affairs	07/15/2008
ADDRESS *(Street, City, State and ZIP Code)* 56 Livingston Ave. Roseland, NJ 07068		**Telephone Number** (862) 740-2719

Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Central Document Room 5901-B Ammendale Road Beltsville, MD 20705-1266	Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.