



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 36,827

Vanda Pharmaceuticals, Inc.  
Attention: Karen McCullough, Ph.D.  
9605 Medical Center Drive, Suite 300  
Rockville, MD 20850

Dear Dr. McCullough:

Please refer to your Investigational New Drug Application (IND) for iloperidone tablets.

We also refer to the meeting between representatives of your firm and the FDA on February 1, 2007. The purpose of the meeting was to discuss the format and content of a proposal for future NDA submission.

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 Kimberly Updegraff, M.S., R.Ph., Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING**  
IND 36,827 Serial # 249 Iloperidone Tablets  
Vanda Pharmaceuticals, Inc  
Pre-NDA Type B Meeting  
February 1, 2007

Participants –

**FDA**

Thomas Laughren, MD	Division of Psychiatry Products Director
Mitchell Mathis, MD	Deputy Director
Ni Aye Khin, MD	Medical Team Leader
Robert Levin, MD	Medical Reviewer
Thomas Oliver, PhD	Chemistry Leader
Peiling Yang, PhD	Statistics Team Leader
Barry Rosloff, PhD	Pharm/Tox Team Leader
Sonia Tabacova, PhD	Pharm/Tox Reviewer
Kimberly Updegraff, MS, RPh	Regulatory Project Manager
Keith Kiedrow, Pharm D	Regulatory Project Manager

**Attendees Representing the Sponsor**

Paolo Baroldi, MD.Ph.D.	Chief Medical Officer
Thomas Copmann, Ph.D.	VP, Regulatory Affairs
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Michael Di Marino	Biostatistician
Karen McCullough, Ph.D.	Director Regulatory Affairs
Deepak Phadke, Ph.D.	VP, Manufacturing
Mihael Polymeropoulos, M.D.	Chief Executive Officer
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Curt Wolfgang, Ph.D.	Clinical Program Head

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**Background:**

Iloperidone is an atypical antipsychotic agent that is under development for the treatment of schizophrenia. Iloperidone was first developed by HMR, who conducted 13 ph 1 and 2 studies. Novartis took over the IND in 1998 and conducted 12 additional ph 1 and 2 studies, as well as 3 short-term ph 3 studies (3000, 3004, 3005), 3 longer-term ph 3 studies, and 1 study with elderly patients with dementia. Vanda took over the IND in 2004 and has conducted 1 additional ph 1 study (1001) and 1 additional ph 3 study (3101). Study 3101 has been completed, but the open-label phase is ongoing and is expected to be completed by March 2007. Thus, the program overall includes 19 ph 1 studies, 7 phase 2 studies, and 7 phase 3 studies. There have been 3 additional studies, including 2 ph 1 studies with alternative formulations and a ph 3 study in elderly patients with dementia (3007). The sponsor is preparing a NDA submission and would like to discuss the format and content of the submission.

As noted, there are 4 adequate and well-controlled ph 3 safety and efficacy studies in schizophrenia (3000, 3004, 3005, and 3101):  
-3000: 3 fixed doses (4,8,12 mg/day vs pbo); US

- 3004: 2 dose ranges (4-8 mg/day and 10-16 mg/day vs pbo); non-US
- 3005: 2 dose ranges (12-16 mg/day and 20-24 mg/day vs pbo); US and non-US
- 3101: 1 fixed dose (24 mg/day) vs pbo; US and non-US

The safety database for iloperidone will include:

- 3046 patients exposed to iloperidone in double-blind phases of phase 2-3 studies
- 1237 patients exposed to iloperidone in open label extensions of phase 2-3 studies (some overlap with the 3046 number)
- 424 patients/subjects exposed to iloperidone in phase 1 studies
- It appears that there will be sufficient longer-term exposures to meet ICH requirements

### **Questions:**

#### **1.1. Outline of the Iloperidone Integrated Summary of Effectiveness**

##### **Background:**

An overview of how Vanda proposes to structure and present the integrated summary of effectiveness for iloperidone tablets is presented in the briefing book.

1. There are five adequate and well controlled studies in the iloperidone development program. Four of these studies (3000, 3004, 3005, 3101) will be pooled for the ISE, whereas one study (B202) will be presented along with the pooled analyses. Does the Division agree that this is acceptable?

**Preliminary Comments:** *Our primary focus will be on individual study results, however, we don't object to your plan for exploratory analyses based on pooling.*

**Discussion at Meeting:** *Given our focus on individual study results, they may reconsider expending resources to prepare an extensive ISE, and we indicated our agreement with this.*

2. Does the Division agree that the proposed dose groupings for the pooled analysis are acceptable for the ISE?

**Preliminary Comments:** *As noted, we don't object to your plan for exploratory analyses based on pooling.*

**Discussion at Meeting:** *No further discussion.*

3. Does the Division agree with the proposal for investigating effectiveness in population subgroups?

**Preliminary Comments:** *We don't object to your plan for investigating effectiveness in population subgroups. However, please note that the purpose of subgroup analyses is to explore the consistency of treatment effects across subgroups. They are not intended for claims in any subgroup. The non-inferiority analysis will also be considered exploratory.*

**Discussion at Meeting:** *They inquired about current division policy regarding a noninferiority approach to maintenance studies in schizophrenia. We indicated that, although we are still open to considering such an approach, we have not completed the work needed to establish a policy change.*

4. The ISE will present results obtained using three approaches for handling missing data: (1) a mixed effects regression model (MMRM); (2) observed cases (OC) [missing data not imputed]; and (3) last observation carried forward (LOCF). This approach will be used for the presentation of data from individual studies and for pooled analyses. Does the Division agree that this approach is acceptable?

**Preliminary Comments:** *We don't object to your plan for exploratory analyses based on pooling. As noted, however, our primary focus will be on individual study results, and for these, we will focus primarily on the protocol-specified primary analysis plans. You should clearly indicate the pre-specified primary analysis and sensitivity analyses in individual study reports.*

**Discussion at Meeting:** *The sponsor indicated that they plan to conduct MMRM analyses for sensitivity purposes, and we indicated that this would be acceptable.*

5. Overall, does the Division agree with the proposed presentation of efficacy data described in the briefing package?

**Preliminary Comments:** *For all efficacy studies in support of approval, please include in your NDA submission (a) all raw as well as derived variables in .xpt format, (b) SAS programs that produced all efficacy results, (c) SAS programs by which the derived variables were produced from the raw variables, (d) a list of IND/serial submission numbers for all protocols, amendments, SAPs, and all related meetings.*

*In the NDA submission, include the exploratory data analysis results for the whole genome scan following your proposal for statistical review.*

**Discussion at Meeting:** *The sponsor indicated that they will address these requests and will also provide preliminary data from the whole genome scan.*

## 1.2. Outline of the Iloperidone Integrated Summary of Safety

### **Background:**

An overview of how Vanda proposes to structure and present the integrated summary of safety for iloperidone is presented in the briefing book.

6. Does the Division agree that it is acceptable to pool safety data from clinical studies conducted by Novartis and Vanda for an integrated analysis, and present the safety data from clinical studies conducted by HMR along with, but separate from, the pooled data?

**Preliminary Comments:** *Generally we don't object to this plan, however, we will want deaths and SAEs pooled for ease of access by reviewers.*

**Discussion at Meeting:** *The sponsor noted that combining data across these very different programs would be difficult; however, they indicated that they would be able to provide a tabular listing of such events, along with links to more complete data. We indicated that this would be acceptable.*

7. Does the Division agree that the proposed dose groupings described in Section 4.7 are acceptable for the ISS?

**Preliminary Comments:** *Yes, as previously discussed.*

**Discussion at Meeting:** *No further discussion.*

8. Does the Division agree that the proposal for investigating safety in the demographic subgroups described in briefing package is acceptable for the ISS?

**Preliminary Comments:** *Yes.*

**Discussion at Meeting:** *No further discussion.*

9. Overall, does the Division agree with the proposed presentation of safety data described in the briefing package?

**Preliminary Comments:** *Yes, but with the qualifications noted above. In addition, we have the following comments:*

*-Please separate safety data by controlled vs. non-controlled phases as opposed to combining the two phases. Also, please provide separate safety analyses for the 4-week study versus the 6-week studies, as well as pooling all controlled study data.*

*-We ask that you include patient safety profiles for deaths, SAEs, and discontinuations due to AEs, ECG abnormality, or laboratory abnormality. In addition, we would like patient profiles for instances of "suicidality" or overdose, where overdose is defined as:  $\geq 36$  mg. Alternatively, you may develop an algorithm that would permit a reviewer to easily create a patient profile from the database.*

*-We ask that you include narratives for deaths, SAEs, instances of "suicidality", and overdoses.*

-Please provide a QTc outlier analyses to include:  $QTc \uparrow \geq 30$  msec;  $QTc \uparrow \geq 60$  msec;  $QTc \geq 450$  msec;  $QTc \geq 480$  msec; and  $QTc \geq 500$  msec.

-Please provide adverse events and other safety parameters by dose groups.

-If possible, provide useful descriptions and categorizations for all discontinuations (Note: the classifications "subject choice or withdrew consent" are not useful.).

-List drug exposure in patient-years (for controlled studies combined and non-controlled studies combined).

-Provide vital signs outlier analysis as follows (amended from the proposed criteria):

*Blood pressure:*

- Systolic BP  $\geq 150$  mmHg and  $\uparrow \geq 10$  mmHg
- Systolic BP  $\leq 90$  mmHg and decrease  $\geq 10$  mmHg
- Diastolic BP  $\geq 100$  mmHg; DBP  $\leq 65$  mmHg

*Weight: Change  $\geq 7\%$*

Discussion at Meeting: The sponsor indicated that they will address these requests, and will consider developing an algorithm for generating individual patient safety profiles.

### 1.3. Pharmacology and Toxicology

#### 1.3.1. Acceptance Criteria for Drug Substance Qualified Related Substances

##### Background:

The following question was asked of the Office of New Drug Quality Assessment at the July 13, 2006 pre-NDA CMC meeting. During this meeting, Dr. Ramesh Sood, Branch Chief of the Office of New Drug Quality Assessment, recommended that Vanda present this question at the pre-NDA meeting in order to obtain guidance from the pharmacology toxicology and clinical groups. A copy of the FDA meeting minutes are provided in Appendix F.

Drug substance qualified related substances \_\_\_\_\_ may be produced during the manufacturing of iloperidone drug substance. Acceptance criteria for these substances have been proposed to ensure the safety of iloperidone in humans. The proposed acceptance criteria for the drug substance qualified related substances \_\_\_\_\_

\_\_\_\_\_ respectively. All of these related substances have been qualified through nonclinical toxicology studies. Information regarding the qualified related substances can be found in this briefing package.

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10. Does the Division agree that the proposed acceptance criteria for drug substance qualified related substances \_\_\_\_\_ ) are acceptable for NDA filing?

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Preliminary Comments: Yes.

Discussion at Meeting: No further discussion.

### 1.3.2. Acceptance Criteria for Related Substance Byproduct \_\_\_\_\_

#### Background:

The following question was asked of the Office of New Drug Quality Assessment at the July 13, 2006 pre-NDA CMC meeting. During this meeting, Dr. Ramesh Sood, Branch Chief of the Office of New Drug Quality Assessment, recommended that Vanda present this question at the pre-NDA meeting in order to obtain guidance from the pharmacology toxicology and clinical groups. A copy of the FDA meeting minutes are provided in Appendix F. Related substance byproduct \_\_\_\_\_

\_\_\_\_\_ is an intermediate in the manufacturing of iloperidone drug substance. An acceptance criterion for this byproduct has been established to ensure the safety of iloperidone in humans. The current acceptance criterion for related substance byproduct: \_\_\_\_\_ The rationale for this limit is provided in the briefing package.

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11. The proposed acceptance criterion for related substance byproduct \_\_\_\_\_ is not more than \_\_\_\_\_. Does the FDA agree that the acceptance criterion is acceptable for NDA filing?

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Preliminary Comments: Yes.

Discussion at Meeting: No further discussion.

### 1.4. CTD Format and Electronic Submission

#### Background:

The NDA dossier for iloperidone will be submitted in electronic Common Technical Document (eCTD) format. The proposed format and organization of the eCTD are presented in the briefing book.

12. Vanda is utilizing \_\_\_\_\_ for generation of the eCTD submission. Since \_\_\_\_\_ has successfully submitted a pilot eCTD submission (reference eCTD pilot \_\_\_\_\_), Vanda requests a waiver for the

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requirement of a pilot eCTD submission. Does the Division agree that a pilot eCTD submission is not required for the iloperidone dossier (Section 6.1)?

**Preliminary Comments:** *Yes.*

**Discussion at Meeting:** *No further discussion.*

13. Would the Division like to have Vanda and [redacted] demonstrate the navigation of the iloperidone eCTD?

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**Preliminary Comments:** *Once the NDA is submitted, FDA will decide whether or not additional help will be needed.*

**Discussion at Meeting:** *No further discussion.*

14. Does the Division agree that the datasets to be included in the NDA (Sections 6.2.2 and 6.2.3) are acceptable?

**Preliminary Comments:** *Yes, but refer to response to question 5 above.*

**Discussion at Meeting:** *No further discussion.*

15. Does the Division agree that the table of contents of the planned submission (Section 6.3) is acceptable?

**Preliminary Comments:** *Yes.*

**Discussion at Meeting:** *No further discussion.*

16. Are there specific requests/requirements regarding the format (Sections 6.1 and 6.2) and content (Section 6.3) of this submission that should be considered in addition to those described in this briefing book?

**Preliminary Comments:** *You are reminded that, according to the Executive CAC recommendations (please refer to the ECAC meeting minutes dated July 11, 2006 and faxed to Vanda on July 13, 2006), you are advised to "conduct a carcinogenicity study of iloperidone metabolite P95 since it is a major metabolite in humans and there is a substantial toxicological difference between the parent compound and P95 with regard to P95 capacity for induction of hyperplasia and cellular proliferation in rats that is not seen with the parent drug in the same species at a similar oral dose and duration of treatment."*

**Discussion at Meeting:** *The Sponsor stated that they have begun a range finding study, and expect to have a rat carcinogenicity study underway at the time of NDA filing. The Division's position is that such a study would need to be completed prior to NDA filing since it is essential to an adequate evaluation of the carcinogenic potential of the drug. The Sponsor proposed*

*that, until the carcinogenicity study is completed, the product labeling could describe the findings of hyperplasia seen in the 6 month rat study of the metabolite, and indicate that this could progress to tumors with longer term treatment. The Division stated that it is not inclined to accept this approach since it would be important to determine more specifically what types of tumors actually occurred, and at what doses relative to clinical doses, in a 2 year study; in addition it is possible that tumors unrelated to the hyperplasia seen in the 6 month study could arise. The Sponsor also indicated that they have obtained new data on the mechanism of action of the metabolite; specifically that it is an alpha-1 blocker, and that this action can explain the hyperplasia seen in the 6 month rat study. The Division indicated that convincing mechanistic data, as well as data showing that the proposed carcinogenic mechanism is not likely to occur in humans, would be useful in determining the relevance of the results of a rat carcinogenicity study to humans, but would likely not obviate the need for such a study. The Division stated that the Sponsor may submit any relevant new data and arguments for consideration in support of their view that a carcinogenicity study could be done in phase 4.*

**Conclusions:**

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Vanda Pharmaceuticals, Inc. is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

\_\_\_\_\_  
Kimberly Updegraff, BS, MS, RPh  
Regulatory Project Manager

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 36,827 Serial #248

Vanda Pharmaceuticals  
Attention: Karen McCullough, PhD, Director, Regulatory Affairs  
9605 Medical Center Drive  
Suite 300  
Rockville, MD 20850

Dear Dr. McCullough:

Please refer to the teleconference between representatives of your firm and FDA on November 17, 2006. The purpose of this meeting was to discuss Iloperidone and the proposed/modified SAP for the phase III trial VP-VYV-683-3101.

The official minutes of the 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 Keith Kiedrow, Pharm.D., Regulatory Health Project Manager, at (301) 796-1924.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING**

IND 36827 N248 Iloperidone  
Vanda Pharmaceuticals  
Type B meeting / EOPII  
November 17, 2006

Iloperidone for schizophrenia – discussion of proposed/modified SAP.

Participants –

**FDA**

Thomas Laughren, MD	Division of Psychiatry Products Director
Ni Aye Khin, MD	Medical Team Leader
Robert Levin, MD	Medical Reviewer
Felix Frueh, PhD	Associate Director, Office of Clinical Pharmacology
Peiling Yang, PhD	Biostatistics Team Leader
Fanhui Kong, PhD	Biostatistics Reviewer
Sue-Jane Wang, PhD	Associate Director, Adaptive Design and Pharmacogenomics, Office of Biostatistics
Kimberly Updegraff, RPh, MS	Regulatory Project Manager
Keith Kiedrow, PharmD	Regulatory Project Manager

**Attendees Representing the Sponsor**

Mihales Polymeropoulos, MD	Chief Executive Officer
Paolo Baroldi, MD	Chief Medical Officer
Thomas Copmann, PhD	Vice President, Regulatory Affairs
Christian Lavedan, PhD	Head of Discovery
Karen McCullough, PhD	Director, Regulatory Affairs
Curt Wolfgang, PhD	Iloperidone Project Leader
Michael DiMarino	Biostatistician

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**Background:**

The purpose of this meeting is to discuss the statistical analysis plan (SAP) for study 3101, a 4-week study comparing iloperidone (24 mg/day) vs ziprasidone (160 mg/day) and placebo (2:1:1 randomization) in patients with acutely exacerbated schizophrenia. The primary objective is to compare the efficacy of iloperidone and placebo in patients overall, using MMRM as the primary analysis. If there is a statistically significant separation on this comparison, the key secondary objective is to compare the efficacy of iloperidone and placebo in patients lacking the CNTF FS63Ter polymorphism (-). Sensitivity analyses will include LOCF, OC, and pattern mixture models, if necessary. The sponsor also plans to explore iloperidone's efficacy in patients with and without this polymorphism.

The sponsor also plans to conduct a whole genome analysis on consenting patients. They will split the sample so that genetic factors associated with response can be identified in the first sample and then checked for confirmation in the second.

**Questions:**

**Questions regarding calculation of outcome variables**

1. Does the Division agree with the baseline-as-a-covariate MMRM model proposed in the SAP?

**Preliminary Comments:** *Yes.*

**Discussion at Meeting:** *No further discussion occurred.*

2. Does the Division agree with the methodology proposed for pooling sites?

**Preliminary Comments:** *Yes.*

**Discussion at Meeting:** *No further discussion occurred.*

3. Does the Division agree that alternative analytic methods proposed to address possible non-normal efficacy data are acceptable?

**Preliminary Comments:**

*In principle, we discourage the practice of using the same data set for model selection (such as power transformation determined from the internal trial data you proposed) and testing. Alternatively, we suggest that you use data from previous trials to decide what transformation would be appropriate if the normality assumption is not met.*

*Although it will be a matter of NDA review whether or not the normality assumption is considered violated, we encourage you to pre-specify a clear rule for determining violation of normality to avoid potential controversies (partially due to multiple choices and their impact on type I error), should data normality appear ambiguous.*

**Discussion at Meeting:**

*The sponsor proposed a randomization test based on the MMRM model with at least 1000 simulations to derive the p-value. This will be considered as a sensitivity analysis to address potential violation of data normality. We accepted this proposal.*

4. Does the Division agree that the analysis plan defined in the SAP is acceptable to address the primary and secondary objectives?

**Preliminary Comments:**

*The SAP for the primary objective (the ITT population) appears acceptable.*

*For the step-down primary objective, comparison of iloperidone vs. placebo will be made in those patients whose genotype status is determined as CNTF FS63Ter(-)/Ter(-). You state that missing CNTF genotypes will not be imputed in instances where the collected DNA sample is not of sufficient quality. You should be aware that, if your goal is to include information based on this analysis into labeling, you need to ensure the DNA sample quality for proper determination of genotyping results. Assessment of iloperidone effect in this setting will be a review issue.*

*We would like to remind you that we view your secondary objective, i.e., a descriptive evaluation of potentially differential responses between CNTF FS63 Ter(-)/Ter(-) vs. the remaining three genotypes in the iloperidone treated patients alone, as exploratory only. This evaluation does not address the effectiveness of iloperidone vs. placebo. Thus, it*

would not qualify for a comparative labeling claim (See September, 2006 meeting minutes).

*You need to clearly state in the protocol that the CNTF FS63 Ter (-) genotype refers to CNTF FS63 Ter(-)/Ter(-) and CNTF FS63 Ter(+) genotype refers to the remaining three genotypes as clarified in the previous meeting.*

*Analyses for other efficacy variables (such as CGI-S, CGI-I, PANSS factors, etc.) will all be considered exploratory.*

**Discussion at Meeting:**

*The sponsor indicated that they will submit details regarding the quality of collected DNA samples at the time of their NDA submission. The sponsor agreed that their secondary objective is a descriptive evaluation and is exploratory. The sponsor also clarified that definition of CNTF FS63 Ter(+) vs. Ter(-) can be found in page 9 of the submission.*

**Question regarding analysis of whole genome scans**

5. The SAP proposes methods for identifying and confirming associations between genetic markers and efficacy parameters in whole genome scans of patients enrolled in the VP-VYV-683-3101 study. Does the Division agree that these methods are acceptable and could provide one source confirmatory evidence for a specific marker being predictive of iloperidone efficacy?

**Preliminary Comments:**

*Please clarify the exploratory/confirmatory association study between genetic markers and efficacy parameters in whole genome scans. It isn't clear from the description that this would represent a comparison between iloperidone treated patients vs. placebo treated patients for each SNP to be categorized according to your approach. As described in the proposal, the comparison is between AA vs. (AB+BB), BB vs. (AB+AA), AB vs. (AA+BB), and where the top and bottom 30% of the pooled iloperidone treated and placebo treated patients are selected for such analysis. This approach would be of regulatory interest only if each comparison would be between iloperidone treated patients vs. placebo treated patients.*

**Discussion at Meeting:**

*The sponsor stated that the study in question had been completed.*

*The sponsor described and stated they would submit an alternative proposal that would include a comparison between iloperidone treated patients vs. placebo treated patients. We reiterated that, if they hoped to propose labeling language based on the results of this analysis, it would be important to make this clear in the NDA, and consideration of this proposal would be a review issue.*

**Conclusions:**

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Vanda Pharmaceuticals is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

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Keith Kiedrow, Pharm.D.  
Regulatory Project Manager

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/s/

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Thomas Laughren  
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Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of New Drugs

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** July 13, 2006

<b>To:</b> Karen McCullough, Ph.D.	<b>From:</b> Adele Seifried
<b>Company:</b> Vanda Pharmaceuticals	OND-IO
<b>Fax number:</b> (301) 294-1900	<b>Fax number:</b> 301-796-9855
<b>Phone number:</b> (240) 599-4509	<b>Phone number:</b> 301-796-0535

**Subject:** Response to Carcinogenicity Special Protocol Assessment Request - Final CAC Report - IND 36,827

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**Total no. of pages including cover:** 5

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**Comments:**

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**Document to be mailed:**       YES       NO

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**Executive CAC**

Date of Meeting: July 11, 2006

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair  
Joseph Contrera, Ph.D., OPS, Member  
John Leighton, Ph.D., DDOP, Alternate Member  
Barry Rosloff, Ph.D., Team Leader  
Sonia Tabacova, Ph.D., Presenting Reviewer

Author of Draft: Sonia Tabacova, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

IND # 36827 No.207

Drug Name: Iloperidone

Sponsor: Vanda Pharmaceuticals

Background: This application was originally submitted by Novartis in August 2002 and contains the final report of a 26-week rat study with the iloperidone metabolite, P95-12113 (Study No. 017013, 8/16/2002). P95 is a major metabolite in humans (42% of total drug-related products), while in rats P95 is only 1.2% of total exposure. Rodent plasma exposure to metabolite P95 (based on P95 AUC values) at the highest iloperidone doses employed in rodent carcinogenicity studies of the parent compound (16 mg/kg/day, rat; 10 mg/kg/day, mouse) represented merely 1-5% of human plasma exposure to P95 upon iloperidone oral administration at the MRHD. The objective of the P95 26-week rat study was to "identify potential effects of P95 on cellular proliferation, which could be associated with pre-neoplastic activity of the metabolite". This issue was discussed in a meeting with the full CAC on May 11, 2001. At the time of the meeting, the 26-week rat study with P95 metabolite had not been completed. In the minutes of the meeting, the CAC concluded that "An optimal test of the carcinogenic potential of iloperidone for humans has not been conducted... Provided there are no significant toxicological differences for P95 and iloperidone and no indication of hyperplasia in the ongoing P95 study (the 26-week P95 rat toxicology study), and provided the sponsor is able to confirm the level of exposure to P95 as projected based on extrapolation, further studies are not warranted to assess iloperidone's carcinogenic potential". In the comments, it was stated that if the 26-week P95 rat toxicology study "demonstrates abnormal proliferative responses in non-target tissues, then the study results should be returned to CAC for consideration of additional toxicity testing". Subsequently, the sponsor finished the 26-week P95 study and found evidence of hyperplasia and/or cellular proliferation by routine histology and BrDU labeling in five tissues (mammary, pituitary, pancreas, thyroid and ovary), as documented in this submission. The sponsor (Novartis) stated that "no additional non-clinical testing to address the carcinogenic potential of iloperidone or its metabolites was planned", requested that FDA "determine the adequacy of the existing carcinogenicity program", and asked if "the CAC and the Division concur that the carcinogenic potential of iloperidone and its metabolites have been adequately addressed and that the product could be appropriately labeled for carcinogenic risk based on the available data". This submission has not been reviewed by CAC because the original sponsor (Novartis) suspended

the development of iloperidone shortly (a few months) after the submission of the 26-week P95 study in August/2002. At present, another sponsor (Vanda Pharmaceuticals) has the drug and wants to know the CAC and Division's opinion.

#### Summary of Results

The 26-week rat study of P95 oral toxicity employed doses of 50 and 500 mg/kg/day, corresponding to plasma exposure (AUC 0-24) of about 2 to 3x and 150 to 400x the human AUC at the MRHD at the LD and HD, respectively. Non-neoplastic proliferative changes (detected by either routine histology and/or by immunohistochemical staining for cell proliferation) occurred in the mammary gland, ovary, anterior pituitary, thyroid gland and endocrine pancreas. The sponsor attributes these changes largely to a "reduction of dopamine-mediated inhibition of prolactin secretion by the pituitary, leading to raised serum prolactin", but this contention is not supported by the results of the study that failed to find prolactin increases (as determined twice in the course of treatment – at wks 14 and 26). Neither is it supported by P95 pharmacological characteristics, i.e., P95 dopaminergic activity is "much less" than that of parent drug and P95 "does not contribute to the primary pharmacological activity of iloperidone" (as stated by sponsor). Moreover, proliferative changes were not observed in 26-week toxicity study with the parent compound (iloperidone) in the same species, despite of the parent's much higher dopaminergic activity. In the 6-month iloperidone toxicity study in rat [at oral (gavage) doses of 12, 24, and 48 mg/kg/day], no proliferative microscopic changes were reported; the primary finding upon microscopic examination was a dose-related vacuolation of adrenal glandular epithelium; other microscopic findings included fatty infiltration of bone marrow, inflammation of the prostate, and testicular degeneration. (Dr. Freed, P/T Memorandum to IND 36827 No.57/8/4/1995). Prolactin was not determined in that study. Carcinogenicity studies of iloperidone in mice (2.5, 5, 10 mg/kg/day) and rats (4, 8, 16 mg/kg/day) "produced no evidence of a tumorigenic response of relevance to humans"; there was an increased incidence of malignant mammary gland tumors in mice at LD that, according to the sponsor, "was not considered to be a direct effect but secondary to the pharmacological inhibitory activity on the dopamine receptor"; serum prolactin measured in wk 4 was increased in the male and female mice in all dose groups (IND 36 827, No 191/4/11/2001, Briefing Book for CAC Meeting). Therefore, there is a substantial toxicological difference between the parent compound and P95 metabolite with regard to P95 cellular proliferation capacity that is not seen with the parent drug, at a similar dose level and duration of treatment, although iloperidone reaches tissues that are targets of P95 proliferative effect, such as pancreas, and pituitary [iloperidone tissue distribution studies showed "significant levels of radioactivity" in these tissues (Dr. Freed, P/T Memorandum to IND 36827 No. 57/8/4/1995)].

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#### Executive CAC Recommendations and Conclusions:

\* The Committee concurred that the full potential for carcinogenicity of the major human iloperidone metabolite P95 has not been adequately tested. A follow-up study in rats is appropriate. Generally 1 species would be sufficient for the metabolite.

\* The Committee advised that the sponsor conduct a carcinogenicity study of iloperidone metabolite P95 since it is a major metabolite in humans and there is a substantial toxicological difference between the parent compound and P95 with regard to P95 capacity for induction of hyperplasia and cellular proliferation in rats that is not seen with the parent drug in the same species at a similar oral dose and duration of treatment.

\* While iloperidone 2-year carcinogenicity assessment did not show histopathology findings of tumorigenic response of relevance to humans, its acceptance was contingent on the 6-month P95 study not showing a potential for cellular proliferation - but it did show such a potential. The findings of the 6-month P95 study suggest a mechanism that could be relevant to tumorigenic activity in humans.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

cc:\n  
/Division File, DPP  
Barry Rosloff, Ph.D./Team leader, DPP  
Sonia Tabacova, Ph.D./Reviewer, DPP  
Keith Kiedrow, Pharm.D./CSO/PM, DPP  
/ASeifried, OND IO

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David Jacobson-Kram  
7/13/2006 09:45:43 AM  
PHARMACOLOGIST

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** September, 7, 2005  
**LOCATION:** Woodmont II - 4<sup>th</sup> Floor Conference Room  
**APPLICATION:** IND 36,827 / Iloperidone  
**SPONSOR:** Vanda Pharmaceuticals, Inc.  
**TYPE OF MEETING:** End of Phase II  
**MEETING CHAIR:** Tom Laughren, M.D.  
**MEETING RECORDER:** Steve Hardeman, R.Ph.

### FDA ATTENDEES

Tom Laughren, M.D., Acting Director, Division of Psychiatry Products  
Bob Levin, M.D., Medical Officer, Division of Psychiatry Products  
Steve Hardeman, R.Ph., Acting Chief, Project Management Staff, Division of Psychiatry Products  
Ray Baweja, Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader  
Peiling Yang, Ph.D., Statistical Team Leader  
Fanhui Kong, Ph.D., Statistical Reviewer

### SPONSOR ATTENDEES

Mihales Polymeropoulos, M.D.  
Curt Wolfgang, Ph.D.  
Rosa Torres, Ph.D.  
Karen McCullough, Ph.D.  
Thomas Copmann, Ph.D.

### BACKGROUND:

Iloperidone is a 5HT<sub>2</sub>/D<sub>2</sub> antagonist being developed for schizophrenia that has a long history due to problems with marginal efficacy and a potential for QTc prolongation similar to that seen with the drug ziprasidone. The sponsor now plans an additional short-term trial that they hope will be sufficient to support the filing of an NDA in support of this drug. (See minutes of 4-28-05 meeting with this sponsor to discuss the status of this program.)

### Proposed Study (VYV-683-3101)

Study VYV-683-3101 is a double blind, randomized, parallel group, multicenter, 4-week study involving three treatment groups, utilizing a 2:1:1 randomization [iloperidone (24 mg/day); ziprasidone (160 mg/day); placebo]. Dosing would be B.I.D. The total sample size would be n=600 (with groups of 300 for iloperidone, and 150 each for ziprasidone and placebo). The sample would include patients with acute exacerbations of schizophrenia or schizoaffective disorder (DSM-IV). Titration to the targeted fixed doses would occur during week 1, and patients would be maintained at these target doses for the final 3 weeks. The primary objectives would be to compare iloperidone 24 mg/day vs. placebo, and to compare efficacy in patients lacking the CNTF FS63Ter mutation vs. those who have it. The proposed primary efficacy variable is the difference between iloperidone and placebo group in slope of the regression line from baseline to LOCF for PANSS total score. The primary model would be MMRM.

- We reminded them that they would need full specification of the MMRM model, as well as justification for its use in this setting, along with sensitivity analyses and verification of the MAR assumption (We referred them to the minutes for the 7-27-05 cancelled meeting for detailed statistical advice.).

We had several additional statistical comments:

- We inquired about the plan to use slope as the primary measure for analysis. We noted that this is an unusual choice, and strongly recommended that they utilize the more traditional measure of change from baseline. They clarified that they, in fact, plan to use change from baseline as their primary measure.
  - We asked for clarification that their ITT sample would also require baseline assessment, and they confirmed this.
  - Regarding an interaction term in the model, they clarified that this was not planned for the primary model, but rather, would be used in exploratory analyses.
  - Finally, we reminded them that they needed to submit a final SAP well-before completion of the trial. They agreed to provide the SAP by June 2006.
2. **Given the evidence discussed in Section 3, and assuming a positive outcome in VYV-683-3101, does the Division agree that the data are sufficient to support the claim that iloperidone is indicated for the treatment of schizophrenia?**

Comment: We indicated that one additional positive short-term trial would likely be sufficient for filing, however, we could not provide a definitive answer on whether or not longer-term efficacy data would be needed at the time of filing until after our Fall 2005 Psychiatry Drug Advisory Committee (PDAC) meeting on this topic. In any case, we indicated that we would very likely take iloperidone to a PDAC, given the safety concerns with this drug.

3. **Does the Division agree that the data described in Section 4 of the briefing book are sufficient to demonstrate long-term maintenance of antipsychotic effect of iloperidone?**

Comment: We indicated that, at this time, we do not agree with the interpretability of active-controlled maintenance studies, or the use of historically obtained placebo relapse rates, as a basis for meeting the requirement for longer-term efficacy data. We informed the sponsor that we intend to bring the issue of the need for longer-term efficacy data for chronic psychiatric disorders, as well as the appropriate design of studies to address longer-term efficacy, to a Fall 2005 meeting of the PDAC, and that we cannot provide definitive advice on this question until after that meeting. They indicated they will participate in that meeting and will argue for the acceptability of active controlled comparisons and use of historical placebo relapse rates in this setting, given what they consider to be a strong consistency across trials of various antipsychotics of lower relapse rates in patients who are randomized to active drug and a much higher relapse rate in those who are randomized to placebo. We acknowledged that there is active debate about this issue, and expressed a willingness to listen to arguments. In the meantime, we advised them to plan for an adequate and well-controlled trial to address this question, in anticipation of a different standard than has been in place in the past. They wanted agreement that we would accept the results of a maintenance trial after the filing of an application, if the results could be submitted within 3 months of filing the application. We indicated that it was difficult to accept data from an independent trial after the original filing of an application, for review during that original cycle, but they could also make an argument at that time.

4. Does the Division agree that (a) a partial waiver is appropriate for iloperidone for patients below the age of ten, and (b) it is appropriate to defer the assessment the effects of iloperidone in patients between 10 and 18 until assessments in adults have been completed?

Comment: We indicated our agreement with a waiver for iloperidone for patients below the age of 13, and a deferral for the assessment of the effects of iloperidone in patients between 13 and 18 until assessments in adults have been completed.

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Thomas Laughren  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 36,827 Serial #233

Vanda Pharmaceuticals  
Attention: Karen McCullough, PhD, Director, Regulatory Affairs  
9605 Medical Center Drive  
Suite 300  
Rockville, MD 20850

Dear Dr. McCullough:

Please refer to the meeting between representatives of your firm and FDA on September 12, 2006. The purpose of this meeting was to discuss Iloperidone and the Statistical Analysis Plan (SAP) for the phase III trial VP- VYV -683-3101.

The official minutes of the 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 Keith Kiedrow, Pharm.D., Regulatory Health Project Manager, at (301) 796-1924.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING**  
IND 36,827 Serial #233 Iloperidone  
Vanda Pharmaceuticals  
EOPII / Type B meeting  
September 12, 2006

Participants –

**FDA**

Thomas Laughren, MD	Division of Psychiatry Products Director
Mitchell Mathis, MD	Deputy Director
Ni Aye Khin, MD	Medical Team Leader
Robert Levin, MD	Medical Reviewer
Peiling Yang, PhD	Statistics Team Leader
HM James Hung, PhD	Director, Division of Biometrics I, Office of Biostatistics
Kooros Mahjoob, PhD	Deputy Director, Division of Biometrics I, Office of Biostatistics
Yeh-Fong Chen, PhD	Biostatistics Reviewer
Sue-Jane Wang, PhD	Associate Director, Adaptive Design and Pharmacogenomics, Office of Biostatistics
Felix Frueh, PhD	Associate Director, Office of Clinical Pharmacology
Kimberly Updegraff, RPh	Regulatory Project Manager
Keith Kiedrow, PharmD	Regulatory Project Manager

**Attendees Representing the Sponsor**

Curt Wolfgang, PhD	Clinical
Mihael Polymeropoulos, MD	Clinical
Paolo Baroldi, MD, PhD	Clinical
Michael DiMarino	Biostatistics
Christian Lavedan, PhD	Clinical Pharmacogenetics
Thomas Copmann, PhD	Regulatory Affairs
Karen McCullough, PhD	Regulatory Affairs

b(4)

**Background:**

Iloperidone is an atypical antipsychotic agent that is under development for the treatment of schizophrenia. A pivotal phase 3 study (VP-VYV-683-3101) is currently underway, and the sponsor is seeking advice on how best to address in the statistical analysis plan (SAP) missing data. Study 3101 is a 4-week placebo-controlled study of iloperidone in acutely exacerbated schizophrenic patients. Vanda has proposed an MMRM model for analysis of the efficacy data and wants to obtain FDA feedback on their specific approach.

**Questions:**

**Background for Question 1**

The first key issue pertains to methods of adjusting for differences in the outcome variable (e.g. severity of patients' symptoms) at baseline prior to treatment. When patients are randomly assigned to treatments, on average—that is, over repeated studies—the treatment groups will be similar in every respect. In any particular study, however, random differences in

severity will be seen among the groups, and adjusting for these differences in an appropriate way will improve the precision of estimated treatment effects. Current literature on likelihood-based mixed-model repeated-measures (MMRM) analysis describes a variety of methods of adjusting for differences at baseline; for example, Fitzmaurice, Laird and Ware (*Applied Longitudinal Analysis*, 2004, Wiley, Section 5.7) describe the pros and cons of four different strategies. Those authors prefer to regard the baseline measurement as the first outcome in each patient's longitudinal series, rather than the more traditional method of using the baseline measure as a fixed covariate. If the baseline measurement is used as outcome, one could estimate the change in mean response (end of study minus baseline) for each treatment group. The intent-to-treat (ITT) effect of a particular drug relative to placebo could then be defined as the change in mean response among the patients receiving that drug, minus the change in mean response for the patients receiving the placebo.

#### **Questions:**

**Question 1:** Does the Division agree that, in an MMRM analysis of data from a trial studying the efficacy of an antipsychotic, it is appropriate to treat each patient's baseline measurement as the first outcome in his or her longitudinal series, and define the ITT effect of a particular drug as the difference between (a) the change in mean response from baseline to end of study for patients receiving the drug, and (b) the change in mean response from baseline to end of study for patients receiving the placebo?

***Preliminary Comments:*** *We cannot respond to this question without more detailed information. Please provide a step by step explicit mathematical model(s) to clarify your analysis; in particular, the specifics of the terms in " $Y_i = X_i\beta + Z_i b_i + \varepsilon_i$ ", the mathematical expressions for the estimator of the treatment effect, and its variance. Please compare your approach with the commonly used MMRM approach (using change from baseline as the response variable and including the baseline score as a covariate) and justify the advantages and disadvantages of your approach over the other. In addition, please create two examples to illustrate your approach and compare with the other. For example, one could demonstrate that all patients are completers (no missing values) and the other could have some dropouts and missing values. Also, please include detailed SAS codes for both examples.*

***Discussion at Meeting:*** *The sponsor agreed to our preliminary comments and indicated that they have reached a conclusion that either approach is acceptable. Thus, they agreed to use the commonly used MMRM approach (i.e., using baseline measurement as a covariate in the model) as their primary analysis. We suggested that they could use the new approach as an exploratory analysis. However, we still asked that they provide more details on the model they have selected.*

#### **Background for Questions 2-5**

Standard software for MMRM analyses (e.g., SAS PROC MIXED) treat all missing outcomes as if they are ignorably missing or missing at random (MAR), according to the definition of Rubin (1976, *Biometrika*, 63:581-592). The concept of MAR, especially as it pertains to dropout in longitudinal studies, has often been misunderstood. Over the last decade, statisticians have attempted to clarify the issue. Extensive discussion on the meaning of ignorable dropout is provided by Little (1995, *JASA*, 90:1112-1121), Verbeke and Molenberghs (2000, *Linear Mixed Models for Longitudinal Data*, Springer), Fitzmaurice, Laird and Ware (2004, *Applied Longitudinal Analysis*, Wiley) and many others. These authors unanimously

agree that individuals' responses prior to dropout do not—indeed, cannot—provide any evidence against MAR. MAR allows individuals' propensities to drop out to depend in an arbitrary way on outcomes measured at visits up to and including the terminal visit. For example, if a patient drops out of a trial because the treatment received has an unsatisfactory therapeutic effect, and this lack of therapeutic effect is evident in the lack of improvement as measured in the response variable prior to dropout, this would be entirely consistent with MAR. Evidence against MAR does not come from pre-dropout values of the outcome variable being modeled by the MMRM. Rather, evidence against MAR could only come from sources external to the observed data. Given the difficulty in demonstrating the presence or nature of nonignorable dropout, the authors mentioned above unanimously agree that the possibility of MAR in an MMRM analysis cannot be excluded. Indeed, they agree that an analysis assuming on ignorable dropout provides a natural baseline model against which the results of other procedures should be compared.

In contrast to an MMRM, an observed-case (OC) analysis—which omits the subjects who dropped out prior to a given occasion for estimation and testing at that occasion—leads to unbiased estimates if the missing measurements are missing completely at random (MCAR), an assumption that is highly restrictive and typically violated in efficacy trials. An LOCF analysis—which replaces each missing value for each patient by the most recent observed value—is generally inappropriate even under the assumption of MCAR (Molenberghs et al., 2004, *Biostatistics*, 5:445-464). In most circumstances, results from OC and LOCF should not be given the same weight as those from an MMRM, because the assumptions underlying these two procedures are less plausible. Nevertheless, comparing results from these procedures to those from MMRM can be regarded as a simple, readily available sensitivity analysis, as it reveals something about the degree to which the conclusions may be affected by alternative assumptions about the missing values.

Alternative models that assume that missing values are missing not at random (MNAR), and posit a joint distribution for the complete data and mechanism of dropout, may also be useful in sensitivity analyses. Given that these models can be specified in an infinite variety of ways, and the observed data provide no guidance on which model is correct, any of these models is easily criticized as arbitrary and subjective. For example, Demirtas and Schafer (2003, *Statistics in Medicine*, 22:2553-2575) present results from five pattern-mixture models applied to data from a psychiatric trial; these models give exactly the same fit to the observed data but radically different estimates of the primary treatment effect. Relying upon pattern-mixture models in efficacy trials is potentially dangerous, because these models are easily manipulated to produce a desired result. Moreover, the results from a pattern-mixture model are not guaranteed to be plausible. Depending on the method of extrapolation being used, a pattern-mixture model may predict post-dropout responses that are well beyond the range of observed measurements for patients at a given occasion. Despite these shortcomings, pattern-mixture models may be somewhat useful for sensitivity analyses, as they provide additional evidence about the degree to which conclusions may rest on untestable assumptions about missing values.

**Question 2:** Does the Division agree that evidence against ignorable dropout in an MMRM cannot be gleaned from subject's pre-dropout response?

***Preliminary Comments:*** *We generally agree that the observed pre-dropout response values cannot be used directly in any statistical test against the MAR assumption, nor can they be used to justify the MAR assumption. However, the patient profile plots may provide information about the underlying characteristics of the patient outcomes*

*variation. For instance, if the post-randomization total PANSS score is linear with a random slope and patients with positive slopes have high probabilities of dropping out, then the dropout mechanism may depend on the random slope; in this case, MAR may be highly doubtful. Plotting the profiles of the dropout patients will provide some hint of such a type of dropout mechanism, even though the profiles themselves cannot be used to test against MAR assumption directly (not for MAR, either). A better assessment may be accomplished if such plots are combined with the reason for the dropout (if investigators can ask the patients at the time of dropout or through follow up interviews).*

***Discussion at Meeting:*** *The sponsor reiterated their view that the information about the underlying characteristics of the patient outcome patterns gleaned from patient profile plots should not be over-emphasized or overly interpreted. We generally agreed with their concern and said that this would be a review issue but still conveyed that the response profile plots are needed. The sponsor agreed to provide the plots.*

**Question 3:** Does the Division agree that submitting results from an MMRM that assumes ignorable dropout as primary evidence, with results from alternative analyses presented as supplementary evidence, would be appropriate?

***Preliminary Comments:*** *Your proposal for using MMRM as the primary analysis seems reasonable if missingness is ignorable. However, if there is any suspicion that the missing mechanism is non-ignorable during the Agency's review, then MMRM may not be deemed appropriate. In this case, sensitivity analyses will be necessary to assess how the results are influenced by the dropouts.*

***Discussion at Meeting:*** *The sponsor agreed with our preliminary comments.*

**Question 4:** Does the Division agree that LOCF and OC analyses may serve as a primary sensitivity analysis, and that pattern-mixture models may serve as a secondary sensitivity analysis, to help interpret the results from an MMRM?

***Preliminary Comments:*** *All of these methods can be used for sensitivity analysis and secondary analysis. In addition, some nonparametric methods (e.g. ETRANK) may be utilized as a secondary analysis, when the normality assumption for MMRM is doubtful. It is known that, if the outcome distribution is heavily skewed, then MMRM may be invalid. When the primary analysis result is questionable, the decision may need to be made based on the totality of these analysis results. We recognize that every method has underlying unverifiable assumptions.*

***Discussion at Meeting:*** *The sponsor indicated that they had explored data from previous trials and feel confident they will be able to show that the normality assumption is satisfied. Nevertheless, they will pre-specify a detailed non-parametric method in the SAP in case there is doubt about the normality assumption. We asked the sponsor to submit the SAP as soon as possible to ensure sufficient time for our review and for their finalization of the SAP before data unblinding.*

**Question 5:** Does the Division agree that the analysis plan defined in the SAP is accepted to address the primary and secondary objectives?

**Preliminary Comments:** *We generally agree. Some points to consider:*

- *In pooling small sites, you may need to set a lower limit of the number of patients in each site to avoid having unstable efficacy results.*
- *In the Section 4.5 subgroup analysis, the SAP states that the step-down primary objective is to determine the efficacy of iloperidone 24 mg/d in patients with the CNTF FS63 Ter(-) genotype compared to patients treated with placebo with the CNTF FS63 Ter(-) genotype, as measured by the PANSS total rating. Please clarify whether the genetic polymorphism subgroup is based on the presence or absence of the specific CNTF allele or the genotype. If the genotype is considered as stated above, please pre-specify whether you consider the genotype that contains the specific allele, e.g., Ter(-)/Ter(-), Ter(-)/Ter(+) and Ter(+)/Ter(-) or just the homozygous Ter(-)/Ter(-) only.*
- *For the purpose of pre-specified genetic subgroup analysis, please pre-specify the imputation algorithm for the missing data.*
- *In addition to the step-down primary objective, do you intend to test a hypothesis based on the “A key objective” of comparing CNTF FS63Ter (-) genotype vs. CNTF FS63Ter (+) genotype in the iloperidone 24 mg/d treated group only? Note that this is at best only a descriptive summary of the PANSS total rating between the two polymorphism groups within the iloperidone 24 mg/d treated patients.*
- *In the first paragraph of your “background for question 6”, you state “Our current Phase III trial (VP-VYV-683-3101) prospectively confirms the relationship between CNTF and iloperidone efficacy.” We are at the stage of commenting on your proposed SAP. However, the sentence implies that the CNTF association analysis has been completed. Given that there is no interim analysis planned, please clarify the status of the patient enrollment and what other analyses have also been done.*

**Discussion at Meeting:**

- *The sponsor clarified that the trial is not completed yet; the statement in the meeting package indicating the study was complete was a typographical error. However, they did indicate that trial accrual is complete and data lock is to occur sometime in late November or December, 2006. No interim analysis is planned.*
- *Regarding center pooling, the sponsor stated that they changed the pooling algorithm to specify that there must be at least 20 patients per center after pooling. They need to submit their pooling algorithm for review.*
- *The sponsor clarified that the pre-specified subgroup for CNTF is the genotype FS63 Ter(-)/Ter(-). Thus, the step-down primary analysis is the comparison between iloperidone treated patients vs. placebo in those patients whose genotype is FS63 Ter(-)/Ter(-).*
- *The sponsor considers that ‘A key objective’ is to compare between “Ter(-)/Ter(-)” vs. “the remaining three genotypes as a group” within iloperidone-treated patients only and intends to seek a descriptive claim. However, the division noted that the study randomization did not account for stratification by patients’ CNTF status. Thus, the division reiterated that this comparison is only a descriptive summary and is not a randomized comparison. Dr. Laughren stated that the results of such a comparison could not be the basis for a claim in labeling, i.e., it is not causal. .*
- *There is no “missing genetic data, so there is no need for imputation.*

***Additional comments from the Office of Biostatistics: For a genetic subgroup claim, the specific assay used in the clinical trial needs to be pre-specified. Is it an approved diagnostic test that is commercially available? The sponsor indicated that the test used for CNTF FS63 genotyping is 100% accurate. We asked the sponsor to provide data for justification regarding the diagnostic assay performance on sensitivity, specificity and accuracy.***

#### **Background for Question 6**

Vanda's development program, through pharmacogenetics, aims to identify likely responders to iloperidone and provide a possible risk management strategy that ensures physicians can adjust drug dosing as appropriate to minimize side effects. Previous studies have demonstrated an association between *CYP2D6* status and adverse event profiles. A marker of efficacy has also been identified in a Phase III study a gene called *CNTF*, or *ciliary neurotropic factor*. Our current Phase III trial (VP-VYV-683-3101) prospectively confirms the relationship between *CNTF* and iloperidone efficacy. However, to further understanding of genetic markers of iloperidone efficacy and safety, exploratory analyses using whole genome scans (WGS) will also be conducted on samples from consenting patients in the on-going Phase 3 study. Should new markers of iloperidone efficacy or safety be identified, we would like to use the on-going study for both exploratory and confirmatory purposes. The analysis approach to be employed is described below.

Because the WGS analysis is optional for patients participating in VP-VYV-683-3101, the following is an example based on a hypothetical consent rate. Assume 600 patients participating in VP-VYV-683-3101 consent to the WGS analysis. Vanda plans to segregate this sample into 2 groups: Group 1 – the first 300 patients randomized, and Group 2 – the last 300 patients randomized. Because the groups are based on randomization order, patients from each treatment arm will be equally distributed between Groups 1 and 2. Group 1 will be used to identify genetic markers that correlate with response, irrespective of the treatment given. Criteria for determining if a marker associates with efficacy measures will be defined in the SAP. If a marker is identified in Group 1 as being predictive of treatment response, the association will be prospectively tested in Group 2 using the same analysis methods used to identify the marker. If the marker again shows statistical significance (using proper statistical methods), it will be considered prospectively confirmed for response across treatment groups. Based on this confirmation, Vanda will also prospectively test the role of any identified markers in iloperidone-specific response measures through the following step-down objectives: (1) to determine the efficacy of iloperidone 24 mg/d in patients with the genetic markers identified in the WGS analysis compared to all patients treated with placebo, as measured by the PANSS total rating, and (2) to determine the efficacy of iloperidone 24 mg/d-treated patients with the WGS markers as compared with iloperidone 24 mg/d-treated patients lacking the WGS markers, as measured by the PANSS total rating.

Similar types of analyses will be performed as well for key safety measures (i.e. QTc prolongation, EPS, etc.) as defined in the SAP.

**Question 6:** Does the Division agree that (a) with Vanda's approach and (b) the proposed analysis plan would provide evidence of the first prospective analysis of genetic markers of response (efficacy and /or safety) to iloperidone via the whole genome scan?

**Preliminary Comments:** *We acknowledge that you are considering exploratory analyses using whole genome scans to identify additional genetic markers (other than CNTF and CYP2D6) of iloperidone efficacy and safety by controlling false discovery rate for adjusting the multiple testing. In general, it is reasonable to control only the false discovery rate for exploratory purposes.*

*However, we have concerns with your proposal for using the optionally consented genomic data both for exploratory purposes and for confirmatory evidence within the same trial. As indicated in the SAP, the DNA samples are collected through the optional PG protocol for iloperidone-treated and placebo-treated patients. There are many confounding factors, including potential differing characteristics between consented vs. non-consented patients. For example, early withdrawal patients might have consented initially at study randomization with different characteristics as compared to non-consented withdrawals. Unknown confounders that are implicit in the optionally consented PG samples can introduce unknown bias that cannot be assessed. Such a patient selection process results in a convenience sample only and cannot yield a randomized comparison for confirmatory purpose.*

**Discussion at Meeting:** *To summarize the nature of the screening, the plan is that patients will be genotyped with several hundred thousands biallelic SNPs distributed throughout the genome. The total number of SNPs to be explored will rely on those SNPs that pass all quality control steps and the analysis is to be done gene by gene. This clearly states the nature of the exploration. The sponsor acknowledged the Division's concerns about the proposed approach for exploration /confirmation, but would like the Division to re-consider this approach. The sponsor indicated that they plan to submit a new proposal in support of this approach in late November or early December. The Division stated that the submission needs to be much earlier than data lock to allow for sufficient time for review these complicated statistical issues.*

**Conclusions:**

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Vanda Pharmaceuticals is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

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Keith Kiedrow, Pharm.D.  
Regulatory Project Manager

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 36,827

Vanda Pharmaceuticals Inc.  
Attention: Karen McCullough, Ph.D.  
Director, Regulatory Affairs  
9605 Medical Center Drive, Suite 300  
Rockville, MD 20850

Dear Dr. McCullough:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ILO 522A, iloperidone tablets.

We also refer to the meeting between representatives of your firm and the FDA on July 13, 2006. The purpose of the meeting was to discuss Chemistry, Manufacturing and Control (CMC) issues in preparation for New Drug Application (NDA) submission.

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 me at (301) 796-2055.

Sincerely,

*{See appended electronic signature page}*

Scott N. Goldie, Ph.D.  
Regulatory Health Project Manager  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure

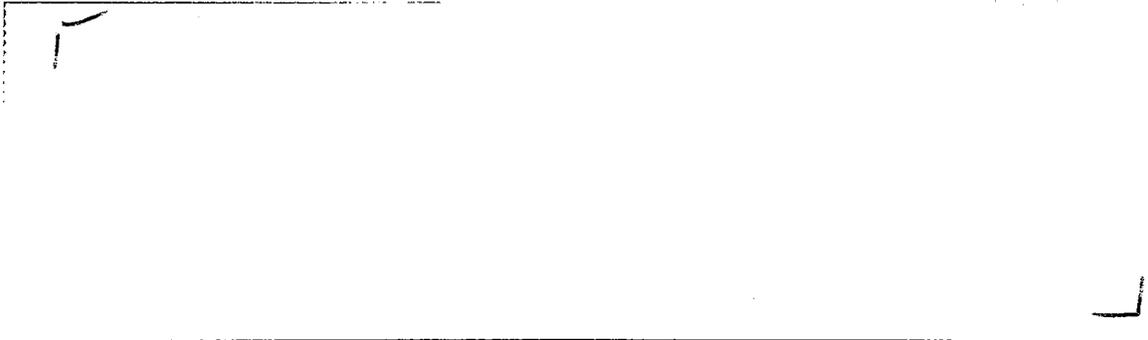


These revisions were collectively submitted to the administrative file on July 11, 2006, received July 12, 2006. FDA provided written responses to all questions outlined in the briefing document in an email from Scott N. Goldie, Ph.D. to Karen McCullough, Ph.D. dated July 12, 2006. Vanda and ONDQA met on July 13, 2006, and the meeting outcomes are recorded below, with the original questions posed and the FDA preliminary responses.

## **DISCUSSION:**

The following are Vanda's questions from the meeting background package and FDA pre-meeting responses, related verbatim. Where further discussion occurred during the meeting, a summary is included in the Meeting Discussion section, along with a summary of the discussion outcomes:

### **Drug Substance**



**FDA Preliminary Response:** Your choice of starting materials is acceptable. In your NDA submission, you will need to describe how each of the starting materials are controlled. Based on your own information and that in the literature, we recommend that you justify your level of control for each residual starting material in the drug substance.

**Meeting Discussion:** Vanda acknowledged and agreed with FDA's recommendations provided. Vanda committed to provide justification for controls of individual impurities in future submissions, including residual starting materials.

2. The current specifications for the intermediates, final intermediates, and iloperidone API are provided in Section 4.2 of this meeting information package. Please advise if FDA concurs that the specifications are appropriate for NDA submission.

**FDA Preliminary Response:** Your drug substance testing seems reasonable at this time, except the melting point is unusually broad and an explanation will be needed to justify your range. You are reminded that all class II solvents (e.g., 1-methyl-2-pyrrolidinone and heptane) should be tested for and properly controlled (as recommended in ICH Q3C).

The adequacy of your intermediate and drug substance specification limits will be determined as part of the NDA review. We recommend that the level of known impurities be expressed as wt% rather than area %.

**Meeting Discussion:** Vanda acknowledged and agreed with FDA's recommendations provided. Vanda committed to provide response factor information in terms of wt% instead of area% to account for changes in instrumental response factors. Vanda would either tighten specification or provide scientific justification for the observed melting point range in future submissions.

3.

\_\_\_\_\_ respectively. All of these related substances have been qualified through nonclinical toxicology studies. Information regarding the qualified related substances can be found in Section 4.3 of this meeting information package. Please advise if FDA concurs that the acceptance criteria are appropriate for NDA submission.

b(4)

**FDA Preliminary Response:** The adequacy of your acceptance criteria is a review issue and will be determined during the NDA review in consultation with the pharm/tox and clinical groups based on the data submitted in NDA.

**Meeting Discussion:** Vanda acknowledged FDA's preliminary response. FDA recommended that the pharm/tox issues raised in this question should be referred to the clinical division for feedback. FDA recommended that Vanda provide strong scientific justification for limits based on qualifying data from batches, and not exclusively from ICH guidance \_\_\_\_\_

b(4)

4. The current acceptance criterion for related substance by product \_\_\_\_\_

\_\_\_\_\_ The rationale for this limit is provided in Section 4.4 of this meeting information package. Please advise if FDA concurs that the acceptance criterion is appropriate for NDA submission.

**FDA Preliminary Response:** The adequacy of your proposed acceptance criterion for related substance byproduct \_\_\_\_\_ is a review issue and will be determined in consultation with the pharm/tox and clinical groups. Based on the information known about byproduct \_\_\_\_\_ please describe what is known about impurity \_\_\_\_\_ [Table 8, page 20], and your plan to adequately control this impurity.

b(4)

**Meeting Discussion:** Vanda acknowledged FDA's preliminary response. FDA recommended that the pharm/tox issues raised in this question should be referred to the clinical division for feedback.

FDA recommended that Vanda provide strong scientific justification for limits based on qualifying data from batches. FDA recommended that these data be included in the submission of this discussion topic to the clinical division.

5. The clinical studies that will be included in the NDA were conducted using Novartis Pharmaceuticals Corporation (Novartis)-manufactured iloperidone API. Following acquisition of the compound and IND by Vanda, the Novartis-manufactured iloperidone API was \_\_\_\_\_ prior to use. The requalified iloperidone API was subsequently used in the production of tablets for clinical studies. Information regarding the requalification of the API can be found in Section 4.5 of this meeting information package. Please advise if FDA agrees with this approach.

b(4)

**FDA Preliminary Response:** Your approach seems reasonable. In the NDA submission, provide the manufacturing date and the retest date for each requalified batch along with the appropriate Certificates of Analysis (CoAs).

b(4)

**Meeting Discussion:** Vanda acknowledged and agreed with FDA's recommendations. Vanda committed to provide the requested data in future submissions.

6. ✓
- Information regarding the stability of iloperidone API can be found in Section 4.6 of this meeting information package. Please advise if FDA agrees with this approach.

b(4)

**FDA Preliminary Response:** In your NDA submission, we recommend that you delineate all the differences of the drug substance manufacturing process at Novartis and \_\_\_\_\_

We recommend you perform a comparative batch analysis of drug substance manufactured at both sites, examining both physical and chemical characteristics (including differences in crystalline and amorphous content).

b(4)

In addition, the effect of crystalline vs. amorphous drug substance forms on drug product performance should be discussed in your NDA submission. Comparative analysis of stability batches from both sites (at same time point) should also be submitted.

**Meeting Discussion:** Vanda acknowledged and agreed with FDA's recommendations. Vanda committed to provide scientific justification regarding the existence or absence of polymorphic forms of the drug substance in the Vanda drug product..

### **Drug Product**

7. The clinical studies that will be included in the NDA were primarily conducted using Novartis-manufactured iloperidone tablets. Following acquisition of the compound and IND by Vanda, the Novartis-manufactured iloperidone tablets were requalified by —, then overencapsulated and used in clinical studies. Prior to use in the clinical studies that included a comparator, the iloperidone tablets were overencapsulated for blinding purposes. Information regarding the requalification and overencapsulation of the tablets is presented in Section 4.7 of this meeting information package. Please advise if FDA agrees with this approach.

b(4)

**FDA Preliminary Response:** Your approach seems reasonable. In the NDA submission, provide the manufacturing date and the retest date for each requalified batch along with the appropriate CoAs. Comparison of dissolution values between iloperidone and overencapsulated iloperidone tablets should be included in your submission.

In addition, we recommend that you delineate all the differences between the drug product manufacturing process at Novartis and commercial supplier, Patheon in your NDA submission. You will need to perform a comparative batch analysis of drug product manufactured at both sites. Comparative analysis of stability batches from both sites should also be included.

**Meeting Discussion:** Vanda acknowledged and agreed with FDA's recommendations. FDA recommended that single point dissolution data may be appropriate, depending upon the scientific justification provided in submissions in consultation with the biopharmaceutics division. FDA recommended that dissolution profiles be submitted to justify the scientific conclusions associated with a single point dissolution analysis.

8.

test. Information regarding identity testing of the tablets is presented in Section 4.8 of this meeting information package. Please advise if FDA agrees with this approach.

**FDA Preliminary Response:** The test for identity by HPLC/UV ( — ) is acceptable as presented in the meeting package.

**Meeting Discussion:** Vanda acknowledged and agreed with FDA's recommendation..

9. The specifications for the drug products are provided in Section 4.9 of this meeting information package. Please advise if FDA concurs that the specifications are appropriate for NDA filing.

**FDA Preliminary Response:** Your drug product testing seems reasonable at this time. You are reminded that each specification needs an appropriate specification limit (acceptance criterion). The adequacy of your drug product specification limits will be determined as part of the NDA review.

**Meeting Discussion:** Vanda acknowledged and agreed with FDA's recommendations. Vanda committed to provide appropriate acceptance ranges for hardness and microbial limit testing in future submissions.

10. The Novartis-manufactured tablets did not have a specification for microbial limit testing. Patheon has added a specification for microbial limit tests. The site-specific registration batches and all subsequent batches of tablets will be tested for microbial limit tests. Information regarding microbial limit testing of the tablets is presented in Section 4.10 of this meeting information package. Please advise if FDA agrees with this approach.

**FDA Preliminary Response:** It is noted that the drug product moisture specification limit is ( ). The adequacy of your acceptance criteria is a review issue and will be determined during the NDA review.

**Meeting Discussion:** Vanda acknowledged and agreed with FDA's recommendations. Vanda committed to provide data to justify the proposed microbial limits with the observed moisture content in the drug product. FDA recommended that the actual drug product stability stress testing data be used to justify the specification limits, and demonstrate meeting acceptance criteria in future submissions.

b(4)

b(4)

11. Patheon will manufacture iloperidone tablets (1, 2, 4, 6, 8, 10, and 12 mg) \_\_\_\_\_

provided in the NDA for the Patheon-manufactured tablet batches. Information regarding stability testing of the tablets is presented in Section 4.11 of this meeting information package. Please advise if FDA agrees with this approach.

**FDA Preliminary Response:** Additional discussion will be needed during the meeting.

**Meeting Discussion:** Vanda described the seven different strengths (1, 2, 4, 6, 8, 10, 12 mg) that were licensed from Novartis. These different strengths are differentiated by color, shape, size, printing and embossing of the dosage forms. Vanda indicated that the \_\_\_\_\_

\_\_\_\_\_ for the purposes of stability testing. FDA agreed, in accordance with the draft stability guidance (Stability Data Package for Registration in Climatic Zones III and IV, Draft February 2002) that the proposed \_\_\_\_\_ was acceptable based on the \_\_\_\_\_

FDA recommended that the justification of: \_\_\_\_\_ be submitted in the future, along with full primary registration batch stability data. Vanda committed to providing \_\_\_\_\_ accelerated site-specific stability batches to bridge between the stability data of Novartis and the Vanda product. FDA stated that the quality and quantity of stability data to demonstrate correlation with the existing Novartis stability data would be the basis of justification of expiry dates for the Vanda product. The comparative analysis of the batches along with stability, manufacturing and packaging data will be critical to justify using the Novartis data to support expiry of the Vanda product. FDA stated that stability data submitted before the 6 month point of the PDUFA review clock would be reviewed within the first cycle, while data submitted after that time point could not be guaranteed to be reviewed in the first cycle.

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b(4)

12. Registration batch stability studies were conducted with Novartis-manufactured tablets. The Novartis stability data include \_\_\_\_\_

b(4)

\_\_\_\_\_ Information regarding container closure of the tablets is presented in Section 4.12 of this meeting information package. Please advise if FDA agrees with this approach.

**FDA Preliminary Response:** Additional discussion will be needed during the meeting.

**Meeting Discussion:** Vanda described their marketing plan for packaging and the existing stability data for the Novartis packaging. Vanda indicated that they were planning to submit data to justify the \_\_\_\_\_

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\_\_\_\_\_  
\_\_\_\_\_  
FDA indicated that Vanda's approach seemed reasonable as presented at the meeting. FDA indicated concerns over the quantity of data for the \_\_\_\_\_ package, and committed to a teleconference with Vanda at a later date to discuss this issue further.

#### **ADDITIONAL COMMENTS AND QUESTIONS:**

1. FDA commented on the lack of photo stability studies in the existing data package. Vanda committed to providing drug product photostability data in the NDA, along with site specific batches for both drug substance and drug product.

2. FDA asked about forced degradation studies of the drug substance and drug product, as these analyses did not appear in the data package. FDA recommended that forced degradation of the drug substance be performed according to ICH guidelines and included in the HPLC method validation package in the NDA submission. Vanda indicated that there has been little degradation observed to this point of the drug product. FDA recommended that drug product be analyzed for photostability, forced degradation and excipient/excipient interactions be addressed and justified in the NDA submission
  
3. Vanda asked if it was reasonable and acceptable to change the supplier of —  
———— (starting material for drug substance) for validation batches. FDA commented that Vanda's vendor qualification program and resulting data used to justify the use of the vendor should be discussed in the NDA. Sufficient data should be provided to justify and bridge between the original supplier and the new vendor.

b(4)

**CONCURRENCE:**

*{See appended electronic signature page}*

Scott N. Goldie, Ph.D.  
Regulatory Health Project Manager for Quality  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment

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this page is the manifestation of the electronic signature.**  
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/s/

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Ramesh Sood  
8/8/2006 08:21:14 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 36,827

Vanda Pharmaceuticals Inc.  
Attention: Karen McCullough, Ph.D.  
Director, Regulatory Affairs  
9605 Medical Center Drive, Suite 300  
Rockville, MD 20850

Dear Dr. McCullough:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ILO 522A, iloperidone tablets.

We also refer to the teleconference between representatives of your firm and the FDA on November 27, 2006. The purpose of the teleconference was to further discuss the acceptability of Vanda's approach to support the marketing of — ntainer closure configurations extending from a Type B Chemistry, Manufacturing and Control (CMC) End of Phase 2 meeting on July 13, 2006.

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

If you have any questions, call me at (301) 796-2055.

Sincerely,

*{See appended electronic signature page}*

Scott N. Goldie, Ph.D.  
Regulatory Health Project Manager  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF NEW DRUG QUALITY ASSESSMENT

<b>Sponsor Name:</b>	Vanda Pharmaceuticals, Inc.
<b>Application Number:</b>	IND 36,827
<b>Product Name:</b>	ILO 522A, iloperidone tablets
<b>Meeting Type:</b>	Type B
<b>Meeting Category:</b>	pre NDA CMC Guidance Meeting
<b>Meeting Date and Time:</b>	November 27, 2006, 2:00 – 2:30 PM EST
<b>Meeting Location:</b>	CDER White Oak – Silver Spring, MD
<b>Meeting Requestor:</b>	Karen McCullough, Ph.D., Director, Regulatory Affairs
<b>Meeting Chair:</b>	Ramesh Sood, Ph.D.
<b>Meeting Recorder:</b>	Scott N. Goldie, Ph.D.
<b>Received Briefing Package</b>	September 29, 2006

**FDA ATTENDEES:**

Division of Pre-Marketing Assessment I

Ramesh Sood, Ph.D.; Branch Chief  
Thomas F. Oliver, Ph.D.; Pharmaceutical Assessment Lead  
Sherita McLamore, Ph.D.; Review Chemist  
Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality

**VANDA ATTENDEES:**

Thomas Copmann, Ph.D.; Vice President, Regulatory Affairs  
Deepak Phadke, Ph.D.; Vice President, Manufacturing  
Manish Anand; CMC Project Manager  
Christon Hill; Senior Manager, Manufacturing

(Consultant to Vanda)

**b(4)**

## 1.0 BACKGROUND

Vanda Pharmaceuticals, Inc. (Vanda) has submitted IND 36,827 for ILO522A, iloperidone tablets, proposed for the treatment of schizophrenia. Karen McCullough, PhD, Director, Regulatory Affairs for Vanda requested a Type B CMC guidance teleconference on September 29, 2006, received on October 2, 2006, to further discuss the acceptability of Vanda's approach to support the marketing of ~~two~~ container closure configurations extending from a Type B CMC End of Phase 2 meeting on July 13, 2006. The meeting request also contained the corresponding briefing package that provided additional information on discussion topics and questions. The teleconference was granted on October 11, 2006. Additional clarification information was requested via email to Karen McCullough from Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality on October 11, 2006, and was supplied on the same day. Preliminary responses to the questions posed in the meeting request/briefing package were submitted via email to Karen McCullough from Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality on November 21, 2006, and archived in the administrative file. The preliminary responses were discussed during the teleconference on November 27, 2006.

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## 2.0 DISCUSSION

2.1

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**Please advise if FDA agrees with this approach.**

2.1.1 **FDA Preliminary Response:** Regarding the \_\_\_\_\_ Bottle: You indicate in the meeting background package that the following stability data will be included from Novartis:

- ✓
- 

b(4)

Your approach, as described in the meeting background package, is acceptable.

2.1.2 **Meeting Discussion:** Vanda accepted the FDA preliminary response. No further discussion occurred during the teleconference.

2.2 ✓

b(4)

Please advise if FDA agrees with this approach.

2.2.1 **FDA Preliminary Response:** Regarding the \_\_\_\_\_ Bottle: You indicate that \_\_\_\_\_ months of long term and accelerated site specific stability data will be provided for the 1, 2, 4, 6, 8, 10 and 12 mg. You further

\_\_\_\_\_ cc bottles. You propose that \_\_\_\_\_ tablets. You point out that the 1-mg tablet in the \_\_\_\_\_ bottle has the \_\_\_\_\_ and therefore represents the worst case scenario. Your approach, as described in the meeting background package is acceptable; however the acceptability of the data is a review issue.

b(4)

2.2.2 **Meeting Discussion:** Vanda accepted the FDA preliminary response. No further discussion occurred during the teleconference.

2.3

configuration will be provided in the NDA at the time of submission. Vanda commits to provide all additional available stability data from the site-specific stability batches during the initial PDUFA 6-month review.

**Please advise if FDA agrees with this approach.**

2.3.1 **FDA Preliminary Response:** The \_\_\_\_\_ bottle has the \_\_\_\_\_ and therefore represents the best case scenario of the \_\_\_\_\_ packaging configurations. Your approach, as described in the meeting background package, is acceptable.

2.3.2 **Meeting Discussion:** Vanda accepted the FDA preliminary response. No further discussion occurred during the teleconference.

2.4

time of NDA submission. Vanda commits to provide all additional available stability data from the site-specific stability batches during the initial PDUFA 6-month review. The Novartis and Patheon stability data will be used to support the registration of the 1-, 2-, 4-, 6-, 8-, 10-, and 12-mg iloperidone tablets in \_\_\_\_\_ packaging.

**Please advise if FDA agrees with this approach.**

2.4.1 **FDA Preliminary Response:** You indicate in the meeting background package that the following stability data will be included from Novartis:

- [redacted]

b(4)

Your approach as described in the meeting background package is acceptable.

2.4.2 **Meeting Discussion:** Vanda accepted the FDA preliminary response. No further discussion occurred during the teleconference.

2.5 The pocket volume of the [redacted] used for the Novartis stability studies was larger than that which will be used for the Patheon site-specific batch stability studies and final commercial presentation. Novartis' development approach was to use the same size [redacted] of all tablet strengths intended to support registration. Novartis' intent was to generate stability data on a worst-case basis and then use size-specific (i.e., smaller) [redacted] for validation and commercial production. Vanda has adopted Novartis' approach and the site-specific batches, as well as all commercial batches, will be packaged in [redacted]

b(4)

**Please advise if FDA agrees with this approach.**

2.5.1 **FDA Preliminary Response:** Your approach, as described in the meeting background package, is acceptable.

2.5.2 **Meeting Discussion:** Vanda accepted the FDA preliminary response. No further discussion occurred during the teleconference.

2.6 The Patheon-manufactured iloperidone tablet registration stability batches were manufactured at a scale not less than [redacted] commercial scale with at least [redacted] tablets manufactured per batch. The plan for packaging includes packaging of at least [redacted]

b(4)

[redacted] The containers will then be placed on stability monitoring.

**Please advise if FDA agrees with this approach.**

2.6.1 **FDA Preliminary Response:** Your approach, as described in the meeting background package, is acceptable.

- 2.6.2 **Meeting Discussion:** Vanda accepted the FDA preliminary response. No further discussion occurred during the teleconference.

### 3.0 ISSUES REQUIRING FURTHER DISCUSSION

During the teleconference, Vanda raised two additional points that were not part of the meeting briefing package. FDA agreed to discuss the points and attempt to provide guidance.

- 3.1 Vanda indicated that the actual volume of the \_\_\_\_\_ bottle depicted in the briefing package is \_\_\_\_\_'s. b(4)

3.1.1 **FDA Preliminary Response:** As this was an issue that was initially raised during the teleconference, no preliminary discussion occurred or was provided.

3.1.2 **Meeting Discussion:** FDA recommended that Vanda provide appropriate scientific justification with the NDA submission to support the arguments regarding the effect on this change in bottle volume on product quality.

3.2

3.2.1 **FDA Preliminary Response:** As this was an issue that was initially raised during the teleconference, no preliminary discussion occurred or was provided.

3.2.2 **Meeting Discussion:** FDA recommended that Vanda provide appropriate scientific justification with the NDA submission to support the arguments regarding the effect of this change in desiccant size on product quality.

### 4.0 ACTION ITEMS

Vanda committed to provide appropriate scientific justification with the NDA submission to support the arguments regarding the effect of the changes in

4.1 Bottle volume.

4.2 Desiccant size.

on product quality.

## **5.0 CONCURRENCE:**

*{See appended electronic signature page}*

Scott N. Goldie, Ph.D.  
Regulatory Health Project Manager for Quality  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment

## **6.0 ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts distributed or used during the teleconference.

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/s/

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Scott Goldie  
11/29/2006 04:00:54 PM

Ramesh Sood  
11/29/2006 04:32:00 PM

MEETING MINUTES  
IND #36,827

Date: November 7, 2002  
Location: Conference Room E; WOC2  
Time: 2:30 – 3:30 PM EST  
Firm: Novartis Pharmaceuticals  
Type: Face-to-Face  
Meeting: Type B; End-of-Phase 2/Pre-NDA Meeting  
Drug: Iloperidone Tablets  
Indication: Schizophrenia  
Meeting Chair: Russell Katz, M.D., Division Director, DNDP, HFD-120  
Meeting Recorder: Paul David, R.Ph., Senior Regulatory Project Manager

**Participants:**

**FDA:**

Drs. Russell Katz, Thomas Laughren, Andrew Mosholder, Judith Racoosin, Teresa Podruchny, and Mr. Paul David

**Novartis:**

Rocco Zaninelli, M.D. Program Leader  
Rajinder Judge, M.D. Neuroscience T.A. Head

Thomas Watson Project Manager  
Roy Dodsworth Neuroscience T.A. Head  
Felix Brugger, Ph.D. Project Leader  
Theresa Gupta, Ph.D. Project Manager

**Novartis Consultant**

External Consultant

b(4)

**Titan Pharmaceuticals**

Frank Valone, M.D. Executive VP, Clinical/Regulatory Affairs  
Victor Bauer, Ph.D. Executive Director, Corporate Development

**Meeting Objective**

Novartis requested this meeting to discuss their pivotal Phase 3 study and, if the study were positive, Agency feedback regarding an NDA submission and the type of labeling that would accompany the drug, if approved.

**Background**

The Agency has previously had four meetings dated November 4, 1998 (End-of-Phase 2), December 20, 2000 (Pre-NDA), June 28, 2001 (Pre-NDA), and November 1, 2001 (Pre-NDA), to discuss the NDA registration of iloperidone in the treatment of schizophrenia. Novartis has completed three Phase 3 studies (Studies 3000, 2004, and 3005) using iloperidone, active control, and placebo. Only one of these studies (Study 3004) demonstrated a statistically significant improvement over placebo by protocol; the other two studies were negative, however, there were clear trends suggesting superiority of iloperidone over placebo. All three studies demonstrated that the active control was at least numerically superior to iloperidone. Another concern associated with the development of this drug was the fact that it prolongs the Q-T interval. The sponsor was previously requested to conduct a clinical study of the effects of iloperidone on cardiac repolarization.

**Purpose:**

Provide Agency feedback on the results of the clinical cardiac study and comment on Novartis's proposed Phase 3 study.

**Discussion:**

1. Novartis opened the meeting by stating that they have concluded that iloperidone has an effect on the QT interval that is similar to that of ziprasidone. The Agency agreed with this assessment.
2. The Novartis representatives clarified a few points regarding the recently completed QTc study for the agency. The QT measurements were obtained at tmax for the parent compound, but this would also be tmax for the metabolite P88 since the two compounds exist in equilibrium. Also, the metabolite P95 is not a HERG channel blocker. The Agency pointed out that higher doses of iloperidone were not studied. For an NDA, there would ideally be additional data on the pharmacokinetics and/or QT effects of iloperidone at higher doses. This additional study would need to incorporate stopping rules for subject safety concerns.
3. 

4. On balance, the Agency indicated that a new drug application for iloperidone (assuming that  is positive) would be fileable but the decision about approvability would be difficult in view of the apparently limited degree of efficacy and the effect on the QT interval. In the event that the drug is eventually approved, the Division would have to consider the labeling implications of the comparative efficacy data. It was also noted that the labeling, if approved, would likely be similar to ziprasidone labeling in regard to Q-T safety issues.

**CONCLUSIONS:**

1. Novartis will reconsider changing the design of their next pivotal study to include an active comparator (optimally, ziprasidone).
2. Novartis will develop an approach to collect data on the pharmacokinetics of iloperidone at higher doses (e.g., 30 or 32 mg) in order to determine whether the plasma levels are comparable to those observed

b(4)

when 24 mg is maximally inhibited. This assessment may be incorporated into the next pivotal study, or conducted separately..

3. Minutes will be provided to sponsor within 30 days from the date of this meeting in accordance with MAPP 4512.1.

\_\_\_\_\_  
**Minutes Preparer**

\_\_\_\_\_  
**Concurrence, Chair (or designated authority)**

**Note to sponsor:** These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

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/s/

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Russell Katz  
12/3/02 08:40:02 AM

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 22-192	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Fanapt Established/Proper Name: iloperidone Dosage Form: tablets		Applicant: Vanda Pharmaceuticals Agent for Applicant (if applicable): N/A
RPM: Kimberly Updegraff		Division: DPP
<p><b>NDA:</b> NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2) Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(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.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>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.</b></p> <p><input type="checkbox"/> No changes                      <input type="checkbox"/> Updated Date of check:</p> <p><b>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.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)		May 6, 2009
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		NA (7/25/08)
❖ 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 <a href="http://www.fda.gov/cder/guidance/2197dft.pdf">www.fda.gov/cder/guidance/2197dft.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application <sup>2</sup> Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 1  <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies  <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC  Comments: _____	
❖ Date reviewed by PeRC (required for approvals only) If PeRC review not necessary, explain: _____	2/11/09
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only)	N/A
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	N/A
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other: Information Advisory

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the 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	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>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.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	N/A
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	N/A
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	N/A
<ul style="list-style-type: none"> <li>NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # _____ and date 10-year limitation expires: _____
<b>❖ Patent Information (NDAs only)</b>	
<ul style="list-style-type: none"> <li>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.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>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.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [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?

Yes     No

(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)?

Yes     No

*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?

Yes     No

(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)?

Yes     No

*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).*

<p>(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?</p> <p>(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).</p> <p><i>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).</i></p> <p><i>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.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	yes
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) AP 5/6/2009 NA 7/25/2008: Located in NA package
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Yes
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	NA
• Original applicant-proposed labeling	Yes
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 9/5/08

<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (full color carton and immediate-container labels) (write submission/communication date at upper right of first page of each submission)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>	NA
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	Yes
<ul style="list-style-type: none"> <li>❖ Labeling reviews (indicate dates of reviews and meetings)</li> </ul>	<input checked="" type="checkbox"/> DMEPA #1 (3/4/2009) #2 (3/26/2009) <input checked="" type="checkbox"/> SEALD 2/10/2009
<ul style="list-style-type: none"> <li>❖ Proprietary Name                             <ul style="list-style-type: none"> <li>• Review(s) (indicate date(s))</li> <li>• Acceptability/non-acceptability letter(s) (indicate date(s))</li> </ul> </li> </ul>	2/11/2009 2/13/2009
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>• Administrative Reviews (e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting) (indicate date of each review)</li> </ul>	Filing Review: 11/9/2007
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (signed by Division Director)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">www.fda.gov/ora/compliance_ref/aip_page.html</a> <ul style="list-style-type: none"> <li>• Applicant in on the AIP</li> <li>• This application is on the AIP                                     <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (indicate date)</li> <li>○ If yes, OC clearance for approval (indicate date of clearance communication)</li> </ul> </li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ 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)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> <li>❖ Postmarketing Requirement (PMR) Studies</li> </ul>	Yes
<ul style="list-style-type: none"> <li>• Outgoing communications (if located elsewhere in package, state where located)</li> </ul>	Emails: 2/11/2009; 4/15/2009 and 4/24/2009
<ul style="list-style-type: none"> <li>• Incoming submissions/communications</li> </ul>	Emails: 2/10/2009; 2/11/2009; 4/15/2009 and 4/24/2009
<ul style="list-style-type: none"> <li>❖ Postmarketing Commitment (PMC) Studies</li> </ul>	Yes
<ul style="list-style-type: none"> <li>• Outgoing Agency request for postmarketing commitments (if located elsewhere in package, state where located)</li> </ul>	Email: 4/15/2009

<sup>4</sup> Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submission documenting commitment	Email: 4/15/2009
❖ Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC ( <i>indicate date; approvals only</i> )	2/11/09
• Pre-Approval Safety Conference ( <i>indicate date; approvals only</i> )	4/17/09
• Regulatory Briefing ( <i>indicate date</i> )	<input checked="" type="checkbox"/> No mtg
• Pre-NDA/BLA meeting ( <i>indicate date</i> )	7/13/2006; 11/27/ 2006; 2/1/2007
• EOP2 meeting ( <i>indicate date</i> )	11/7/2002; 9/7/2005; 9/12/2006; 11/17/2006
• Other (e.g., EOP2a, CMC pilot programs)	7/11/2006 (CAC); 9/10/2008; 3/16/2009
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	5/6/2009 7/25/2008 Located in NA package
Division Director Summary Review ( <i>indicate date for each review</i> )	3/27/2009 7/11/2008 Located in NA package
Team Leader Review ( <i>indicate date for each review</i> )	Located in NA package: 6/26/2008
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	Located in NA package 6/26/2008
• Clinical review(s) ( <i>indicate date for each review</i> )	Located in NA package 6/25/2008
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Safety update review	Located in NA package 6/25/2008
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Yes (6/25/08 review)
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	Located in NA package QT Review: 2/29/2008
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ Risk Management	<input checked="" type="checkbox"/> None
• Review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	
• REMS Memo ( <i>indicate date</i> )	
• REMS Document and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	Located in NA package 6/18/2008 (DSI)

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	Located in NA package 6/1/2008 (Statistical review) 6/9/2008 (Pharmacogenetics review)
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	1/15/2009 Located in NA package 7/10/2008
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	Located in NA package 5/15/2008
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• Tertiary Pharmacology Review (indicate date for each review)	Located in NA package 7/22/2008
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	Located in NA package 6/30/2008
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	Located in NA package 1/22/2008
❖ ECAC/CAC report/memo of meeting	Located in NA package 3/25/2008
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	Located in NA package 6/24/2008
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) (indicate date for each review)	1/12/2009 Located in NA package 5/1/2008 6/23/2008
• BLAs only: Facility information review(s) (indicate dates)	<input checked="" type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each)	<input checked="" type="checkbox"/> Not needed

<i>review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Located in NA package CMC review dated 5/1/2008
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed (per CMC memo dated 6/24/08) <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i></li> </ul>	Date completed: 1/11/2008 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> <li>• BLAs: <ul style="list-style-type: none"> <li>○ TBP-EER</li> <li>○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i></li> </ul> </li> </ul>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

### NDA REGULATORY FILING REVIEW (Including Memo of Filing Meeting)

NDA # 22-192 Supplement # NA Efficacy Supplement Type NA

Proprietary Name: Under review  
Established Name: Iloperidone  
Strengths: 1,2,4,5,8,10,12 mg tablets

Applicant: Vanda Pharmaceuticals, Inc.  
Agent for Applicant (if applicable): NA

Date of Application: 9/27/2007

Date of Receipt: 9/27/2007

Date clock started after UN:

Date of Filing Meeting: 11/9/2007

Filing Date: 11/26/2007

Action Goal Date (optional): 7/27/2008

User Fee Goal Date: 7/27/2008

Indication(s) requested: Treatment of Schizophrenia

Type of Original NDA: (b)(1)  (b)(2)   
AND (if applicable)

Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S

P

Resubmission after withdrawal?

Resubmission after refuse to file?

Chemical Classification: (1,2,3 etc.) 1

Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES  NO

- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:

- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES   
This application is: All electronic  Combined paper + eNDA   
This application is in: NDA format  CTD format   
Combined NDA and CTD formats

- Does the eNDA, follow the guidance?  
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES   
**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES, \_\_\_\_\_ Years NO   
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES  NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES  NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO
- PDUFA and Action Goal dates correct in tracking system? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. Correct

List referenced IND numbers: 60,113 ; 36,827

- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s) Date(s) September 7, 2005; November 17, 2006; September 12, 2006; November 7, 2002; NO   
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s) Date(s) February 1, 2007; July 13, 2006; June 28, 2001; November 1, 2001 NO

If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) CAC May 11, 2001 NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?  
N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO  NA

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to EA officer, OPS? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO

- If a parenteral product, consulted to Microbiology Team?    NA    YES        NO

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: 11/9/2007

NDA #: 22-192

DRUG NAMES: Iloperidone

APPLICANT: Vanda Pharmaceuticals, Inc.

BACKGROUND: New Molecular Entity

Iloperidone is a psychotropic agent belonging to the chemical class of piperidinyl-benzisoxazole derivatives. Iloperidone has a high affinity for 5HT<sub>2a</sub>/5HT<sub>1a</sub> receptors in humans and acts as an antagonist at selected dopaminergic, serotonergic, and adrenergic receptors. The clinical development of iloperidone was initiated by Hoechst Marion Roussel (HMR) in 1990 under IND 36,827. In 1998, Novartis Pharmaceutical Corporation/Novartis Pharma AG (Novartis) licensed iloperidone (IND 36,827) and continued clinical development until 2004, at which time, Vanda licensed iloperidone and completed clinical development of iloperidone tablets for the treatment of schizophrenia.

ATTENDEES:

Tom Laughren  
Robert Levin  
Donghao Lu  
Phillip Dinh  
Peiling Yang  
Andre Jackson  
Dianne Tesch  
Michelle Chuen  
Ni Khin  
Sue Jane Wang  
Barry Rosloff  
Gwen Zornberg  
Kelly Kelm  
Ray Baweja  
Kavneet-Ripi Kohli-Chhabar  
Kim Updegraff

ASSIGNED REVIEWERS (including those not present at filing meeting) :

**Discipline/Organization**

Medical:

Secondary Medical:

Statistical:

Pharmacology:

Statistical Pharmacology:

**Reviewer**

Michelle Chuen

Peiling Yang

Sonia Tabacova



- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5.  Convey document filing issues/no filing issues to applicant by Day 74.

Kimberly Updegraff, R.Ph., M.S.  
Regulatory Project Manager