

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-977

APPROVAL LETTER



NDA 21-977

New River Pharmaceuticals Inc.
Attention: Suma Krishnan, M.S., M.B.A., R.A.C.
2200 Kraft Drive, Suite 2050
Blacksburg, VA 24060

Dear Ms. Krishnan:

Please refer to your new drug application (NDA) dated December 6, 2005, received December 6, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vyvanse (lisdexamfetamine dimesylate) 30 mg, 50 mg, and 70 mg Capsules.

We acknowledge receipt of your submissions dated December 22, 2006, and January 22 and 24 and February 1, 7, 8, and 16, 2007.

Your submission dated December 22, 2006, constituted a complete response to our December 21, 2006, action letter.

This new drug application provides for the use of Vyvanse (lisdexamfetamine dimesylate) Capsules for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6-12 years of age.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text enclosed to this letter.

Additionally, we have the following comments and recommendations:

Labeling

1. Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide, immediate container and carton labels). Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, designate this submission "SPL for approved NDA 21-977". Approval of this submission by FDA is not required before the labeling is used.
2. Vyvanse requires the distribution of a Medication Guide under 21 CFR 208 in order to prevent serious adverse effects, inform patients of information concerning risks that could affect their decision to use or continue to use the drug, and/or assure effective use of the drug.

3. Submit as described above, a Medication Guide that is identical in content and format to the enclosed Medication Guide. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for every patient who is dispensed Vyvanse. Therefore, format the proposed Medication Guide in a manner that will assure its appropriate distribution to patients and include a plan to ensure distribution. In addition, submit proposed container and/or carton labels for Vyvanse that include a prominent and conspicuous instruction to provide the Medication Guide to each patient dispensed the drug. The label must state how the Medication Guide is provided (e.g., affixed on the container, provided with the product, etc.).

Chemistry Manufacturing and Controls

1. A retest period of [redacted] for drug substance batches manufactured at both manufacturing sites, [redacted] is granted.
2. An expiration date of 24 months for Vyvanse capsules, 30 mg (manufactured using [redacted] [redacted]), 50 mg and 70 mg packaged as 100 count in 60 cc/[redacted] bottles is granted.

Office of Clinical Pharmacology

We acknowledge your agreement to adopt the following final dissolution method and specifications for all three capsule strengths, 30 mg, 50 mg, and 70 mg:

Apparatus:	USP Apparatus 2 (paddle)
Paddle Speed:	50 RPM
Medium:	900 ml of 0.1 N HCL
Specification:	Q=[redacted]% in 15 minutes

Division of Medication Errors and Technical Support

The Division of Medication Errors and Technical Support (DMETS) acknowledges your revisions to the labels and labeling as per our previous recommendations. However, we have the following additional recommendation for the revised label.

Container Labels

The established name is printed in a light grey color that is difficult to read. Please use a bolder font or darker color for the established name in order to improve visibility and readability.



Pediatric Research Equity Act (PREA) Requirements-Studies Waived and Deferred

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 to 5 years (neonates and young children). We are deferring submission of your pediatric studies for ages 13 to 17 years (children and adolescents) until three years from the date of approval of this NDA.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

Post Marketing Commitments

1. Deferred Pediatric Studies Under PREA

You are required to assess the safety and effectiveness of lisdexamfetamine dimesylate as a treatment for Attention Deficit Hyperactivity Disorder in pediatric patients ages 13 to 17.

Final Report Submission: three years from the date of this letter

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment must be clearly designated “**Required Pediatric Study Commitments**”.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Psychiatry Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The Med Watch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

The final scheduling of this product by the Drug Enforcement Administration under the Controlled Substances Act is in progress, but not yet complete as of the date of this letter. We note your

commitment dated February 16, 2007, not to market this drug product until scheduling is finalized. We further note that, upon final scheduling, appropriate revisions should be made as necessary to the package insert, the patient-package insert, and the product labeling by submitting a supplement to your NDA.

If you have any questions, call LT Felecia Curtis, R.N., Regulatory Project Manager, at (301) 796-0877.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment (Labeling)

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

/s/

Robert Temple
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-977

APPROVABLE LETTER 1



NDA 21-977

New River Pharmaceuticals
Attention: Suma Krishnan, M.S., M.B.A., R.A.C.
1861 Pratt Drive, Suite 1090
Blacksburg, VA 24060

Dear Ms. Krishnan:

Please refer to your new drug application (NDA) dated and received December 6, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NRP 104 (lisdexamfetamine dimesylate) 30 mg, 50 mg, and 70 mg Capsules.

We acknowledge receipt of your submissions dated October 13, 24, November 17, 20 and 27, December 1 and 4, 2006.

Your submission dated October 24, 2006, constituted a complete response to our October 6, 2006, action letter.

This new drug application provides for the use of NRP 104 (lisdexamfetamine dimesylate) Capsules, for the treatment of attention deficit hyperactive disorder (ADHD) in children 6-12 years of age.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

Chemistry Manufacturing and Controls

1. In order to determine an acceptable retest period for drug substance batches manufactured at the [REDACTED] facility, please provide at least [REDACTED] month stability data, including data for identified and [REDACTED] impurities, for [REDACTED] additional batches manufactured at the facility.
2. Continue specifying [REDACTED] purity as a quality attribute of the drug substance and drug product. Additionally, optimize the [REDACTED] method to demonstrate a limit of detection (LOD) for [REDACTED], which will allow control of this impurity in the drug substance batches at or below the proposed level of [REDACTED].

3. In order to determine an acceptable expiry for drug product, please provide the 15-minute dissolution data for all primary stability batches of 30 mg, 50 mg and 70 mg strength drug product to demonstrate compliance with the dissolution specification of $Q=$ [redacted] in 15 minutes.
4. In order to determine an acceptable expiry for 30 mg strength drug product manufactured with [redacted], please provide stability data for [redacted] additional batches or a justification that reliance on stability data for [redacted] of 30 mg capsules is sufficient.

In addition, we ask that, in your response, you address the following issues. In some instances this will require only an acknowledgement. In other instances, only a brief update will be needed to cover the period since your last response, or a statement that no new information is available.

Clinical Pharmacology:

We ask that you acknowledge your agreement to the following final dissolution method and specification for all three capsule strengths:

Apparatus: USP Apparatus 2 (paddle)
Paddle Speed: 50 RPM
Medium: 900 ml of 0.1 N HCL
Specification: $Q=$ [redacted] in 15 minutes

Chemistry Manufacturing and Controls

1. In consideration of your agreement with the Agency recommendation of $Q=$ [redacted] in 15 minutes for dissolution, please update the drug product specification. Furthermore, we ask that you update the Description in the drug product specification to agree with that found in the How Supplied section of the Package Insert.
2. Your request for [redacted] should be proposed as a post-approval supplement.
3. For completeness, please provide batch information, *e.g.*, size, batch numbers and certificates of analysis, for the drug substance batches manufactured by both suppliers where levels of [redacted] were monitored.

Risk Management Plan (RMP)

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Foreign Regulatory Update/Labeling

We require a review of the status of all NRP 104 (lisdexamfetamine dimesylate) actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If NRP 104 (lisdexamfetamine dimesylate) has been approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for NRP 104 (lisdexamfetamine dimesylate) along with English translations when needed.

World Literature Update

Prior to the approval of NRP 104 (lisdexamfetamine dimesylate), we require an updated report on the world archival literature pertaining to the safety of NRP 104 (lisdexamfetamine dimesylate). We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of NRP 104 (lisdexamfetamine dimesylate). The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Labeling

Please submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert). The attached labeling is the labeling mutually agreed to in our 11-29-06 teleconference, with the exception of two additional modifications noted in this document.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

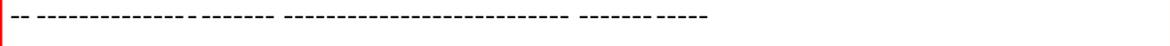
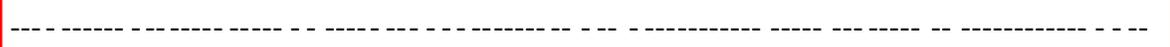
Additionally, we remind you that upon a final scheduling action by the DEA your label will be required to bear the symbol designating the schedule in which NRP 104 is controlled.

Proprietary Name and Container Label

The Division of Medication Errors and Technical Support (DMETS) find the proprietary name “Vyvanse”, acceptable. However, our approval of the proprietary name is tentative

based upon the final date of NDA approval. If final approval of this application extends beyond February 2007, the name will be reevaluated by DMETS.

Additionally, we have the following recommendations pertaining the container label 30 mg, 50 mg, and 70 mg (100-Count)

1. 
2. 
3. 
4. 
5. 

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved and scheduling is complete.

If you have any questions, call LT Felecia Curtis, R.N., Regulatory Project Manager, at (301) 796-0877.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment (Labeling)

15 Page(s) Withheld

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Draft Labeling

Deliberative Process

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/s/

Robert Temple
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-977

APPROVABLE LETTER 2



NDA 21-977

New River Pharmaceuticals
Attention: Suma Krishnan, M.S., M.B.A., R.A.C.
1861 Pratt Drive, Suite 1090
Blacksburg, VA 24060

Dear Ms. Krishnan:

Please refer to your new drug application (NDA) dated and received December 6, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NRP 104 (lisdexamfetamine dimesylate) 30 mg, 50 mg, and 70 mg Capsules.

We acknowledge receipt of your submissions dated February 15 and 22, March 16, April 11 and 18, May 18, 22, and 30, June 6, 9, 16, 22 and 29, July 14, 18 and 25, August 2, 14, 15, 22 and 29, September 1, 14, 15 and 19, 2006.

This new drug application provides for the use of NRP 104 (lisdexamfetamine dimesylate) Capsules, for the treatment of attention deficit hyperactive disorder (ADHD) in children 6-12 years of age.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

Office of Clinical Pharmacology

We ask that you agree to the following final dissolution method and specifications for all three capsule strengths:

Apparatus:	USP Apparatus 2 (paddle)
Paddle Speed:	50 RPM
Medium:	900 ml of 0.1 N HCL
Specification:	Q= ----- in 15 minutes

Chemistry Manufacturing and Controls

1. Please provide the updated drug substance and drug product specifications including all changes reflected in the amendment dated September 1, 2006, and received September 5, 2006. This amendment responded to the agency's information request letters dated August 24 and 26, 2006. The specification for ~~-----~~ should remain in the updated drug substance specification.
2. You have proposed a retest period of ~~---~~ months for the drug substance manufactured at ~~-----~~ based on the real time ~~---~~ month data. Please make clear whether you are also

proposing the same retest period for drug substance manufactured at [REDACTED]. Provide stability data for the drug substance batches manufactured at [REDACTED] facility so that an appropriate retest date can be assigned to this material. Please refer to ICH Q1A(R2) and ICH Q1E for the amount of stability data needed for assigning a retest date.

3. You have provided no stability data for the 30 mg capsules manufactured using [REDACTED] drug substance [REDACTED]. Please provide long-term and accelerated stability data for 30 mg NRP104 capsules generated from [REDACTED] drug substance [REDACTED].
4. Please tighten the drug substance specification limit for impurities [REDACTED] [REDACTED] [currently, NMT [REDACTED] (area %) each], and for [REDACTED] (currently, NMT [REDACTED] (area %), or provide the data to demonstrate that the acceptance limits are qualified [include the release testing results (e.g., CoAs) of the batches used for qualification]).
5. The Certificate of Analysis of the Lot #3037652 ([REDACTED] Lot 1001D) provided in the amendment of September 1, 2006, demonstrates different results of testing for several organic volatile impurities and residual solvents from that provided in the original NDA submission. Please clarify which results are correct, and why these two CoAs show different results.
6. The acceptance criteria for any single related substance peak of \leq [REDACTED] in the drug product stability specification is not acceptable since the qualification threshold for degradation products in 70 mg capsules (once-a-day treatment) is limited to a maximum of [REDACTED] of total daily intake of the impurity which in this case will be equivalent to [REDACTED] (refer to ICH guidance, Q3B: Impurities in New Drug Products). Please tighten the acceptance limit for this parameter in the drug product stability specification to NMT-[REDACTED]. Refer to decision tree in attachment 3 of ICH Q3B(R) for guidance to identification and qualification of a degradation product.
7. Based on the information provided in the executed batch record for 30-mg NRP104 capsules (Batch #3048382R), the more specific description is provided for the imprinting on the capsules, i.e., [REDACTED] [REDACTED] Please include this specific description of the capsules in the drug product specification.

Bottle Labels

Clinical

1. Among the data on proportions of patients from study 301 meeting certain laboratory test outlier criteria provided in your June 28, 2006 submission, you neglected to include data for proportions meeting outlier criteria for LDH ($\geq 3x$ ULN) and creatine kinase ($\geq 2x$ ULN). Please provide these data.
2. The inclusion criteria for your trials included: “meets DSM-IV-TR criteria for a primary diagnosis of ADHD combined type or predominantly hyperactive-impulsive subtype based on a detailed psychiatric evaluation which reviews the DSM-IV-TR criteria”. Based on your protocol, it appears that a K-SADS-PL was performed. Please clarify if the ADHD diagnosis was based on the K-SADS-PL interview.
3. For Study 301, we ask that you break out certain common adverse events by the following subgroups: age 6-9 vs. 10-12; male vs. female; white vs. nonwhite. The following are the adverse events of interest: upper abdominal pain, decreased appetite, dizziness, dry mouth, irritability, insomnia, nausea, vomiting, and decreased weight.
4. Please provide narratives for the cases of neutropenia and chest pain noted in Appendix Table 6.12 of the Summary of Clinical Safety as adverse events associated with treatment discontinuation.
5. According to our calculations based on Appendix Tables 5.1, 5.2, and 5.3 of the Summary of Clinical Safety, total exposures were 404, and included 348 pediatric patients. In the ADVERSE EVENTS section of your proposed labeling, you state, -----

and 56 healthy adult subjects). Of these, 358 pediatric patients...” Please explain this discrepancy.

Risk Management Plan (RMP)

We note that you have proposed -----. The Controlled Substance Staff (CSS) has recommended that lisdexamfetamine be placed into Schedule II of the CSA based on their review of the abuse potential in human and preclinical studies. The final CSA Schedule of this drug is will be determined by the Drug Enforcement Agency (DEA).

If lisdexamfetamine is controlled as a Schedule II product, your proposed RMP appears sufficient. However, we have the following recommendations to clarify and improve your surveillance plan:

• -----

• -----

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Draft Labeling

Deliberative Process

We request that you amend your application with alternative proprietary names and following review by the Division of Medication Errors and Technical Support, we will forward their recommendation.

Safety Update

Our assessment of the safety of NRP 104 (lisdexamfetamine dimesylate) is based on our review of all safety information provided in your original and subsequent submissions, including your safety update dated April 11, 2006 (data cut-off of January 16, 2006). Please provide a final serious events update to include serious adverse events up to a more recent cutoff date.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved and scheduling is complete.

If you have any questions, call LT Felecia Curtis, R.N., Regulatory Project Manager, at (301) 796-0877.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
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Deliberative Process

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/s/

Robert Temple
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