CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-977

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

1.3.5 Patent and Exclusivity

1.3.5.1 Patent Information (Form FDA 3542a)

In the opinion of New River Pharmaceuticals Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs. (21 CFR 314.50 (i) (*ii*))

NRP104 is the subject of two U.S. pending patent applications. On June 1, 2004, New River Pharmaceuticals Inc. filed U.S. Patent Application No. 10/857,619, titled "Abuse Resistant Lysine Amphetamine Compounds" and U.S. Patent Application No. 10/858,526, titled "Abuse Resistant Amphetamine Compounds".

On June 1, 2004 New River Pharmaceuticals Inc. filed a Patent Cooperation Treaty (PCT) that was assigned Application No. PCT/US04/17204.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
67,482

NAME OF APPLICANT / NDA HOLDER
New River Pharamceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ACTIVE INGREDIENT(S)	STRENGTH(S)
Lisdexamfetamine dimesylate	30 mg, 50 mg, 70 mg

DOSAGE FORM
Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent

d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

FORM FDA 3542a (7/03)

Page 1

PSC Media Arts (301) 443-6740 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
Suma	November 23rd 01

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Suma Krishnan	
Address 1861 Pratt Drive, Suite 1090	City/State Blacksburg, VA
ZIP Code 24060	Telephone Number 540-953-0237
FAX Number *(if available)* 540-953-3407	E-Mail Address *(if available)* skrishnan@nrpharma.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 3542a (7/03)

EXCLUSIVITY SUMMARY

NDA # 21-977 SUPPL # HFD # 130

Trade Name Pending

Generic Name Lidexamfetamine Dimesylate 30, 50, 70 mg Capsules (NRP-104)

Applicant Name New River Pharmaceuticals

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: LT Felecia Curtis
Title: RPM
Date: 8/19/06

Name of Office/Division Director signing form: Thomas Laughren, M.D.

Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Thomas Laughren
10/1/2006 01:38:41 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-977 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: 12/6/05 **Action Date:** 10/6/06 **HFD** 130

Trade and generic names/dosage form: NRP104 (lisdexamfetamine dimesylate) Capsules

Applicant: New River Pharmaceuticals, Inc **Therapeutic Class:** Attention Deficit Hyperactive disorder (ADHD)

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: ADHD

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

XNo: Please check all that apply: X **Partial Waiver** X **Deferred** ____ **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg** _____	**mo.** _____	**yr.** 0	**Tanner Stage** _____
Max _____	**kg** _____	**mo.** _____	**yr.** 5	**Tanner Stage** _____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:** Difficult to accurately diagnosis and treat children in this age range

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr.__13___ Tanner Stage_____
Max_____ kg_____mo._____ yr.__17___ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **X Adult studies ready for approval**
- ☐ **Formulation needed**

Other: Efficacy for this indication not yet established in the adult population.

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr.__6___ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__12___ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
LT Felecia Curtis, RN, Regulatory Project Manager

cc: NDA 21-427
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Felicia Curtis
8/18/2006 11:10:32 AM

1.3.3 Debarment Certification

I, Suma Krishnan, Vice President of Product Development, on behalf of New River Pharmaceuticals Inc. hereby certifies that New River Pharmaceuticals Inc. 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. (Section 306(k)(1) of the Act)

Suma

November 14th 05

Suma Krishnan, M.S., M.B.A., R.A.C.
Vice President, Product Development
New River Pharmaceuticals Inc.
1861 Pratt Drive
Suite 1090
Blacksburg, VA 24060
(540)953-0237

Date

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-977	Efficacy Supplement Type SE-	Supplement Number	
Drug: NRP-104 (Lisdexamfetamine Dimesylate) 30, 50, & 70 mg Capsules		Applicant: New River Pharmaceuticals	
RPM: Felecia Curtis		HFD-130	Phone # 301 796-0877

Application Type: **(X)** 505(b)(1) **( )** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **( )** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	**()** Standard **(X)** Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	12/22/06
❖ Special programs (indicate all that apply)	**(X)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**( )** Paid UF ID number
• User Fee waiver	**(X)** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify) see letter
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **( )** Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	**( )** Yes **(X)** No

• This application is on the AIP	( ) Yes **(X)** No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	**(X)** Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(**X** Verified
• 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.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) 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? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *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 ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	Felecia Curtis, RN RPM, 8/30/06 Michelle Chuen, MD 12/11/06 Yeh-Fong Chen, PhD, Statistical 7/28/06

	Andre Jackson, PhD, Biopharm, 11/21/06 Lyudmila Soldatova, PhD, CMC, 12/8/06 Ikram Elayan, PhD, Pharmacology /Toxicology, 9/27/06
General Information	
❖ Actions	
• Proposed action	( ) AP ( ) TA **(X)** AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes **(X)** Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X)** None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	10/25/06
• Original applicant-proposed labeling	10/25/06
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC 11/30/06 DMETS 11/30/06 DSRCS pending CSS 11/9/06 Pediatric and Maternal 6/23/06 OSE 11/14/06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Adderall, Concerta, Daytrana
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	10/25/06
• Reviews	12/8/06
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	Noted in AE letter
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	See DFS
❖ Memoranda and Telecons	See DFS
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	7/29/04 & 9/21/04
• Pre-NDA meeting (indicate date)	7/21/05 & CMC P-NDA 9/8/05
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Ni Khin, MD, TL 12/12/06
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	12/11/06
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	3/25/05 submitted 6/02
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	8/18/06
❖ Demographic Worksheet *(NME approvals only)*	N/A AE
❖ Statistical review(s) *(indicate date for each review)*	7/28/06
❖ Biopharmaceutical review(s) *(indicate date for each review)*	11/21/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	CSS 11/9/06; scheduling pending
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	9/1/06
• Bioequivalence studies	9/1/06
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	Lyudmila Soldatova, PhD, CMC, 12/8/06
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	9/20/06
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**(X)** Completed **( )** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	9/27/06
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/s/

Felicia Curtis
12/13/2006 09:47:36 AM
CSO

Memo to the file

Date:	February 16, 2007
From:	Colleen LoCicero, Associate Director for Regulatory Affairs Office of Drug Evaluation I
To:	NDA 21-977 Vyvanse (lisdexamfetamine dimesylate) Capsules
Subject:	Need for a preapproval safety conference

Background

New River Pharmaceuticals Inc. is seeking approval of NDA 21-977 for Vyvanse (lisdexamfetamine dimesylate) capsules in the treatment of Attention Deficit Hyperactivity Disorder in children 6-12 years of age. Lisdexamfetamine is a prodrug of dextroamphetamine. When taken orally, lisdexamfetamine dimesylate is rapidly absorbed from the gastrointestinal tract and converted to dextroamphetamine, which is responsible for the drug's activity.

Memo

On February 16th, 2007, I telephoned Dr. Marilyn Pitts, Team Leader in the Division of Drug Risk Evaluation in the Office of Surveillance and Epidemiology, to discuss the need for a preapproval safety conference (PSC) for this NDA. I told Dr. Pitts that because lisdexamfetamine is a prodrug for d-amphetamine, Dr. Temple does not expect its postmarketing safety profile to differ significantly from that of the marketed amphetamines. For this reason, no preapproval safety conference has been scheduled for this application, which is expected to be approved within the week.

Dr. Pitts noted that DDRE provided input on a risk management plan for this drug earlier in its review. She does not expect lisdexamfetamine's postmarketing safety profile to differ significantly from that of the marketed amphetamines and agreed that a PSC is not needed.

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/s/

Colleen LoCicero
2/20/2007 08:15:36 AM
CSO

Curtis, Felecia

From: Suma Krishnan [skrishnan@nrpharma.com]
Sent: Thursday, February 01, 2007 12:10 PM
To: Curtis, Felecia
Subject: RE: NDA 21-977 IR Biopharmaceutical

Hi Felecia,

We accept the dissolution specification suggested by the Agency. I will also send you an official communication.

Thanks

Suma

From: Curtis, Felecia [mailto:Felecia.Curtis@fda.hhs.gov]
Sent: Thursday, February 01, 2007 11:55 AM
To: Suma Krishnan
Cc: Curtis, Felecia
Subject: NDA 21-977 IR Biopharmaceutical

NDA 21-977 **INFORMATION REQUEST LETTER**

New River Pharmaceuticals, Inc.
Attention: Suma Krishnan, MS, MBA
Vice President, Product Development
1861 Pratt Drive
Blacksburg, VA 24060

Dear Ms. Krishnan:

Please refer to your December 22, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lisdexamfetamine dimesylate .

We are reviewing the Biopharmaceutical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

DISSOLUTION: The dissolution data you presented indicates that up to [redacted] months most of the dissolution data meets the S1 specification of each unit not less than Q[redacted]%. This would strongl--- upport all strengths meeting the specification for S2 in which is no unit is less than Q[redacted]%. The agency finds the conducting dissolution at the S2 level is acceptable. We request that you adopt the following final specification for all strengths:

Final dissolution method and specification for all 3 capsule strengths is:

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

If you have any questions regarding this email, please call.

Thanks,
Felecia Curtis

Felecia Curtis, RN, LT, USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
U.S. Food and Drug Administration
10903 New Hampshire Ave Bldg 22 RM 4399 Silver Spring, MD 20993-0002
301-796-0877 felecia.curtis@fda.hhs.gov

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/s/

Felicia Curtis
2/1/2007 12:56:01 PM
CSO

MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology HFD-420; WO22, Mail Stop 4447 Center for Drug Evaluation and Research

To: Thomas Laughren, MD
Director, Division of Psychiatry Products
HFD-130

Through: Linda Y. Kim-Jung, PharmD, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Loretta Holmes, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: January 31, 2007

Subject: DMETS Label and Labeling Review
Drug: Vyvanse (Lisdexamfetamine dimesylate) Capsules
NDA#: 21-977
Sponsor: New River Pharmaceuticals, Inc.

Review #: 2007-183

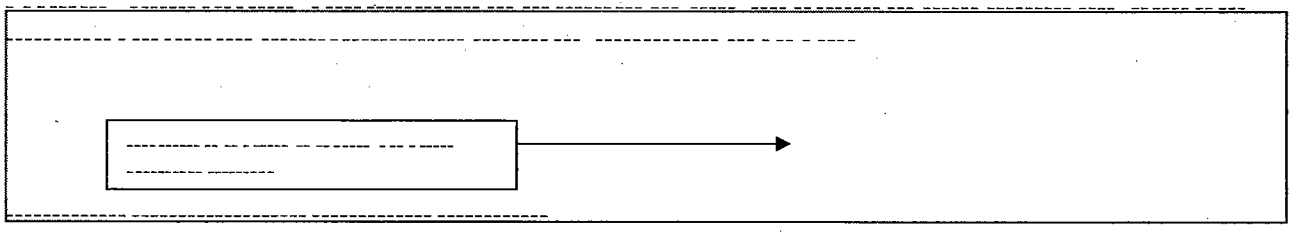
This review is in response to a request from the Division of Psychiatry Products (HFD-130) for a re-review of the proprietary name, Vyvanse (NDA 21-977). Additionally, revised container labels and package insert labeling were provided for review and comment.

The proposed proprietary name, Vyvanse, was found acceptable by DMETS in our previous review of the name (OSE Review 2006-726, dated November 30, 2006). Since the PDUFA date for this application (February 20, 2007) will fall within the 90 day period of our last proprietary name review for Vyvanse, we will not review the name again at this time. However, if approval of this application is delayed beyond 90 days of the signature date of our previous review, the name must be re-evaluated.

After reviewing the revised container labels and package insert labeling, DMETS acknowledges that the sponsor has revised the labels and labeling as per our previous recommendations. However, we have the following additional recommendation for the revised label.

CONTAINER LABELS

-



-

If you have any questions or need clarification, please contact Angela Robinson, Project Manager, at 301-796-2284.

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/s/

Loretta Holmes
2/9/2007 12:52:27 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
2/9/2007 12:54:39 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/9/2007 01:03:24 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 31, 2007

TO: Thomas P. Laughren, M.D., Director
Division of Psychiatry Products

VIA: LT. Felicia Curtis, RN, Regulatory Project Manager
Division of Psychiatry Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm. D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: OSE/DSRCS Review of Medication Guide for lisdexamfetamine dimesylate, NDA 21-977

Background

The sponsor submitted a complete response December 22, 2006, in response to an Approvable Letter issued on December 21, 2006, for lisdexamfetamine dimesylate, NDA 21-977. A previous Approval Letter was issued on October 6, 2006 for this NDA.

Lisdexamfetamine dimesylate is a CNS Stimulant (amphetamine) under review for the treatment of Attention Deficit and Hyperactivity Disorder (ADHD).

The review division requested that DSRCS draft a Medication Guide (MG) for lisdexamfetamine dimesylate for the WARNINGS regarding possible cardiovascular event risk and possible psychiatric adverse events, and to be similar with regard to format and information suggested in the DSRCS drafts of the other ADHD CNS Stimulant MGs.

Two Advisory Committees met (Drug Safety and Risk Management Advisory Committee on February 9, 2006, and the Pediatric Advisory Committee on March 22, 2006) and recommended labeling changes including revised WARNINGS for Serious Cardiovascular Events and Psychiatric Adverse Events and a Medication Guide to adequately warn practitioners and patients about the use of CNS stimulant medications in the treatment Attention Deficit Hyperactivity Disorder (ADHD).

Comments and/or Recommendations

1. See the attached draft lisdexamfetamine Medication Guide. We have drafted and formatted the Medication Guide to a two page document for patient ease of use. We have made it consistent with the PI, and put it in the format specified for Medication Guides in 21 CFR 208.20.

2. Medication Guides should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the Medication Guide.

3. Our draft Medication Guide has a Flesch Kinkaid grade level of 8.5. To enhance comprehension, all patient materials should be written between the 6^{th} and 8^{th} grade reading level.

4. Refer to 21 CFR 201.57(f)(2). The sponsor is required to refer to the Medication Guide in the PI, PRECAUTIONS section, Information for Patients subsection.

5. Comments to the review division are ***bolded, underlined and italicized*** in the attached document.

Please call us if you have any questions.

2 Page(s) Withheld

Trade Secret / Confidential

✓ Draft Labeling

Deliberative Process

Withheld Track Number: Administrative/Correspondence- 1

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/s/

Jeanine Best
1/31/2007 11:56:57 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
1/31/2007 03:45:15 PM
DRUG SAFETY OFFICE REVIEWER

Curtis, Felecia

To: Suma Krishnan

Cc: Curtis, Felecia

Subject: NDA Clinical IR

Hi Suma,

Please refer to your email submission dated 1/22/07 for NDA 21-977 (NRP104 in ADHD). We note that the tables you provided are for the safety populations, whereas the z-score data proposed in labeling are based on the randomized population and treated population for studies 301 and 302, respectively. Please follow the format of tables 8-1 and 8-2 provided in your 8/2/06 submission, adding the age- and sex-normalized percentile values that correspond with the existing z-score data for weight. The patient populations should include only those patients that received drug and had both baseline and endpoint weights.

Thanks!

Felecia Curtis, RN, LT, USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
U.S. Food and Drug Administration
10903 New Hampshire Ave Bldg 22 RM 4399 Silver Spring, MD 20993-0002
301-796-0877 felecia.curtis@fda.hhs.gov

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/s/

Felicia Curtis
1/23/2007 11:14:19 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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 Mrs. Krishnan:

We acknowledge receipt on December 26, 2006 of your December 22, 2006 resubmission to your new drug application for NRP 104 (lisdexamfetamine dimesylate) 30 mg, 50 mg, and 70 mg Capsules.

We consider this a complete, class 1 response to our December 21, 2006 action letter. Therefore, the user fee goal date is February 24, 2007.

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

Sincerely,

{See appended electronic signature page}

LT Felecia Curtis, R.N.
Regulatory project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Felicia Curtis
1/23/2007 11:37:18 AM

Curtis, Felecia

From: Curtis, Felecia
Sent: Friday, January 19, 2007 2:05 PM
To: 'Suma Krishnan'
Cc: Curtis, Felecia
Subject: NDA 21-977 Clinical IR
Importance: Low

Hi Suma,

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NRP104.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

For ease of clinical interpretation, under "Long-Term Suppression of Growth" in the WARNINGS section of your proposed labeling, please modify the following paragraph so that age- and sex-normalized mean weight change from baseline data is stated in percentiles [redacted]:

[redacted]

To support the modified data, please provide your mean change from baseline analyses for weight, adjusting for age and sex by converting to percentiles.

If you have any questions, please email.

Thanks,

Felecia Curtis, RN, LT, USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
U.S. Food and Drug Administration
10903 New Hampshire Ave Bldg 22 RM 4399 Silver Spring, MD 20993-0002
301-796-0877 felecia.curtis@fda.hhs.gov

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/s/

Felicia Curtis
1/19/2007 02:12:49 PM
CSO

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(WO: 22, Mailstop 4447)

DATE RECEIVED: October 30, 2006 **DATE OF DOCUMENT:** October 24, 2006	**DESIRED COMPLETION DATE:** November 30, 2006 **PDUFA DATE:** December 17, 2006	**OSE REVIEW #:** 2006-726

TO: Thomas Laughren, MD
Director, Division of Psychiatry Products, HFD-130

THROUGH: Nora Roselle, Pharm.D., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, RPh., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Linda M. Wisniewski, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: **Vyvanse**
(Lisdexamfetamine Dimesylate Capsules)
30 mg, 50 mg, and 70 mg

NDA# : 21-977

NDA SPONSOR: New River Pharm

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Vyvanse. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name, Vyvanse, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
WO: 22; Mailstop: 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: November 2, 2006

NDA#: 22-977

NAME OF DRUG: Vyvanse
(Lisdexamfetamine Dimesylate Capsules)
30 mg, 50 mg, and 70 mg

NDA HOLDER: New River Pharm

I. INTRODUCTION:

This consult was written in response to a request from the Division of Psychiatry Products (HFD-130), for assessment of the proprietary name, "Vyvanse", regarding potential name confusion with other proprietary or established drug names. The sponsor initially submitted the proposed proprietary names [redacted], for this product, however, they were found unacceptable as a result of DDMAC's objections on February 28, 2006 and March 28, 2006, respectively. The sponsor then submitted the proprietary names [redacted] for this NDA. These names were also found unacceptable on October 5, 2006. [redacted] was found unacceptable as a result of the potential for confusion with [redacted] was found unacceptable as a result of the potential for confusion with [redacted] and [redacted]. For this review the proposed name Vyvanse was submitted for review. Container labels and insert labeling were submitted for review and comment.

PRODUCT INFORMATION

Vyvanse is a pro-drug of dextroamphetamine and has no pharmacological activity. After oral administration, lisdexamfetamine dimesylate is rapidly absorbed from the gastrointestinal tract and gradually converted to dextroamphetamine, which is responsible for the drug's activity. Vyvanse is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) and is for use in children aged 6 to 12 years. Dosage should be individualized according to the therapeutic needs and response of the patient and should be administered once daily at the lowest effective dosage and adjusted in increments of 20 mg at weekly intervals to a maximum recommended dose for children of 70 mg/day. It is supplied in 30 mg, 50 mg, and 70 mg strengths and packaged in bottles of 100 capsules.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Vyvanse to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Vyvanse. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC has no objections to the proposed proprietary name, Vyvanse, from a promotional perspective.

2. The Expert Panel identified twenty proprietary names that were thought to have potential for confusion with Vyvanse. Of the twenty names identified, DMETS found that eight names warranted further evaluation based on look-alike, sound-alike, and product characteristics (See Table 1 on page 4). Upon further review, it was determined that the remaining twelve names are either foreign drugs, are no longer marketed, or lacked convincing look-alike/sound-alike similarities with Vyvanse, in addition to having differentiating product characteristics, such as product strength, indication for use, frequency of administration, route of administration, and/or dosage formulation. Thus, the following names will not be discussed further in this review: Vivarin, Nuvance, Vancenase, Zyprexa, Vanos, Wytensin, Mytelase, Wyamycin, Wyamine, Nystatin, Vivanza, and Zyban.

---

[1] MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], Drugs@FDA, the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.
[4] Phonetic and Orthographic Computer Analysis (POCA).
[5] WWW location http://www.uspto.gov/tmdb/index.html.
[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Look-Alike and Sound-Alike Names Identified by DMETS Expert Panel.

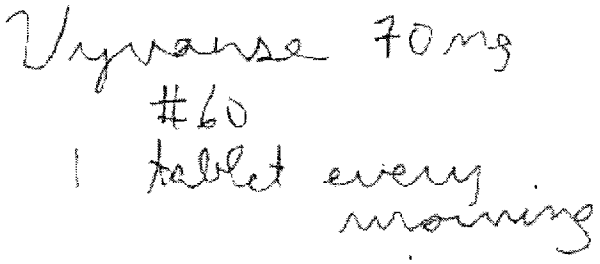
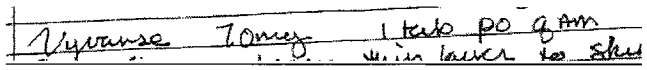
Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Vyvanse	Lisdexamfetamine Dimesylate Capsules 30 mg, 50 mg, and 70 mg	30 mg to 70 mg once daily depending upon symptoms.	NA
Vigamox	Moxifloxacin Hydrochloride Ophthalmic Solution 0.5%	One drop into the affected eye three times a day for seven days.	LA
Nevanac	Nepafenac Ophthalmic Suspension 0.1%	One drop three times a day.	LA
Vivonex Pediatric Vivonex Plus Vivones RTF Vivonex TEN	Enteral Nutrition	As directed.	LA
Vivance	Foreign product. Nutritional supplement in France which is no longer marketed.	No information available.	SA
Vitrase	Hyaluronidase for Injection 6200 units USP/vial	50 units to 300 units subcutaneously.	LA
Vytone	Hydrocortisone-Iodoquinol Cream 1%	As directed.	
Vytorin 10/10 Vytorin 10/20 Vytorin 10/40 Vytorin 10/80	Ezetimibie/Simvastatin Tablets 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, and 10 mg/80 mg	10 mg/10 mg to 10 mg/80 mg daily.	LA
Wydase	Hyaluronidase for Injection 150 units/vial and 1500 units/vial	50 units to 300 units subcutaneously.	LA

*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Vyvanse with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 126 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Vyvanse (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX:  Vyvanse 70mg #60 1 tablet every morning	Vyvanse 70 mg #60 1 tablet every morning
Inpatient RX:  Vyvanse 70mg 1 tab po q am w. in lower to Stat	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Vyvanse, the primary concerns relating to sound-alike and/or look-alike confusion with Vyvanse are Vigamox, Nevanac, Wydase, Vytorin, Vitrase, Vytone, Vivance, and Vivonex.

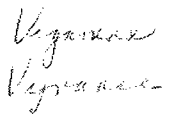
Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspellec/phonetic variations of the proposed name, Vyvanse.

Upon initial review, it is noted that Vivonex is the family trade name for an enteral nutrition product line. When ordering Vivonex, the prescriber must include one of the modifiers (i.e. Plus, etc.) in order to specify the product requested. Therefore, due to the context of use and required modifier, Vivonex is less concerning and will not be further reviewed. Vivance is a foreign product (nutritional supplement in France) which is no longer marketed. Therefore, this name will also not be reviewed further.

The remaining names of concern are discussed in detail below:

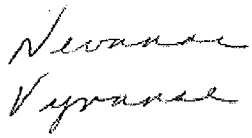
1. Vigamox was identified as a name that has the potential to look similar to Vyvanse when written. Vigamox is indicated in the treatment of bacterial conjunctivitis caused by susceptible Aerobic Gram-positive microorganisms, Aerobic Gram-negative microorganisms, and Chlamydia trachomatis.

   Both names begin with letters that may look similar (Vy vs. Vig). The letters 'nas' and 'mos' may also look similar. These orthographic properties lead to an overall similar orthographic appearance of the two names (see below). However, there are some product differences which may help to differentiate these two products when written. They include dose (30 mg, 50 mg, and 70 mg vs. one drop), frequency of administration (once daily vs. three times a day), strength (30 mg, 50 mg, and 70 mg vs. 0.5%), route of administration (oral vs. ophthalmic), and dosage form (capsule vs. ophthalmic solution). Although Vigamox is supplied in only one strength which may be omitted in an order, orders for Vyvanse would need to include a strength. Thus, the strength may help to differentiate these names when written.



2. Nevanac was identified as a name that may look similar to Vyvanse. Nevanac is indicated in the treatment of pain and inflammation associated with cataract surgery.

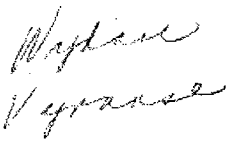
   Both names contain letters that may look similar when scripted (V vs. N and vanse vs. vanac). However, Vyvanse contains a downstroke for the letter 'y' which may help to differentiate it from Nevanac when scripted. There are also some differentiating product characteristics that may help to distinguish these two products when ordered. They include dose (30 mg, 50 mg, or 70 mg vs. one drop), frequency of administration (once daily vs. three times a day), strength (30 mg, 50 mg, and 70 mg vs. 0.1%), route of administration (oral vs. ophthalmic), and dosage form (capsule vs. ophthalmic solution). The downstroke for the letter 'y' in Vyvanse, in addition to the differentiating strengths, will help to differentiate these two products when ordered.



3. Wydase was identified as name that may look similar to Vyvanse when scripted. Although Wydase is a discontinued product, the active ingredient is still available under other proprietary names. Wydase is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs.

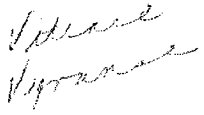
   Both names begin and end with letters that may look similar (Vy vs. Wy and anse vs. ase). However, Wydase contains an upstroke for the letter 'd', whereas Vyvanse has no upstrokes. Additionally, Vyvanse contains seven letters and Wydase contains six. This difference also gives Vyvanse a longer appearance when scripted. There are also some product characteristics which may help to differentiate these two products when ordered. They include dose (30 mg, 50 mg, and 70 mg vs. 50 units to 300 units), frequency of administration (once daily vs. once), strength (30 mg, 50 mg, and 70 mg vs. 150 units/vial

and 1500 units/vial), route of administration (oral vs. subcutaneous), and dosage form (capsule vs. injection). Although the numerals of the doses may overlap at 50 (50 mg vs. 50 units), the unit of measure (units vs. mg) and route of administration will help to differentiate these two products further. Wydase is for intradermal use only and orders for Wydase will most likely include directions to inject a specific amount of solution or number of units. Thus, the upstroke for the letter 'd' in Wydase and longer appearance of Vyvanse, in addition to the differentiating units of measure, frequency of administration and route of administration, will help to distinguish these two product names when written.



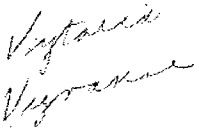
4. Vitrase was identified as a name that may look similar to Vyvanse when scripted. Vitrase is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs.

   Both names begin with the same letter (V) and end in letters that may look similar (anse vs. ase). However, Vyvase contains a downstroke for the letter 'y' and Vitrase contains an upstoke for the letter 't'. These orthographic differences may help to differentiate these two products when written. There are also some product characteristics which may help to differentiate these two products when ordered. They include dose (30 mg, 50 mg, and 70 mg vs. 50 units to 300 units), frequency of administration (once daily vs. once), strength (30 mg, 50 mg, and 70 mg vs. 6200 units/vial), route of administration (oral vs. subcutaneous), and dosage form (capsule vs. injection). Although the numerals of the doses may overlap at 50 (50 mg vs. 50 units), the unit of measure (units vs. mg) and route of administration will help to differentiate these two products further. Vitrase is for intradermal use only and orders for Vitrase will most likely include directions to inject a specific amount of solution or number of units. Thus, the differentiating upstroke for the letter 't' in Vitrase, in addition to the differentiating units of measure, frequency of administration, and route of administration, will help to distinguish these two product names when written.



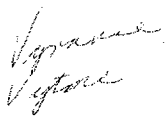
5. Vytorin was identified as a name that may look similar to Vyvanse when scripted. Vytorin is indicated in the treatment of primary hypercholesterolemia and homozygous familiar hypercholesterolemia.

   Both names begin with the same two letters (Vy) and end in letters that may look similar (anse vs. orin). However, Vytorin contains an upstroke for the letter 't', whereas, Vyvanse contains no upstrokes which may help to differentiate these two products when scripted. Both products are orally administered once daily, however, they do differ with regard to dose and strength (30 mg, 50 mg, and 70 mg vs. 10 mg/10 mg, 10 mg/ 20 mg, 10 mg/40 mg, and 10 mg/80 mg). Although orders for Vytorin may be written as one tablet), the strength would have to be written in conjunction with the drug name. Thus, the upstroke for the letter 't' in Vytorin, in addition to the differentiating strengths will help to distinguish these two products when ordered.



6. Vytone was identified as a name that may look similar to Vyvanse when scripted. Vytone is indicated in the treatment of itching associated with eczema or infection.

Both names begin with the same two letters (Vy) and end in letters that may look similar (anse vs. one). However, Vytone contains an upstroke for the letter 't', whereas, Vyvanse contains no upstrokes which may help to differentiate these two names when written. Additionally, Vyvanse has a longer appearance when scripted (see below). There are also some differentiating product characteristics such as dose (30 mg, 50 mg, and 70 mg vs. sufficient amount), frequency of administration (once daily vs. three to four times daily), strength (30 mg, 50 mg, 70 mg vs. 1%), route of administration (oral vs. topical), and dosage form (capsule vs. cream). Although Vytone may be written without a strength and with a general direction of 'Use as directed', orders for Vyvanse would need to include a strength. The upstroke for the letter 't' in Vytone and the longer appearance of Vyvanse, in addition to the product characteristics will help to differentiate these two products when ordered.



III. LABELING, PACKAGING, AND SAFETY RELATED CONCERNS

[redacted]

Appendix A:

Voice	Inpatient Written	Outpatient Written
Vivan	Vyovase	Vynance or Uynance
Vivan	Vyvance	Vynanse
Vivan	Vyvanse	Vynanse
Vivance	Vyvanse	Vynase
Vivance	Vyvanse	Vyvanse
Vivance	Vyvanse	Vyvanse
Vivance	Vyvanse	Vyvanse
Vivance	Vyvanse	Vyvanse
	Vyvanse	Vyvanse
	Vyvanse	Vyvanse
	Vyvanse	Vyvanse
	Vyvanse	Vyvanse
	Vyvanse	Vyvanse
	Vyvanse	Vyvanse
		Vyvanse

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/s/

Linda Wisniewski
11/30/2006 01:37:19 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/30/2006 01:40:42 PM
DRUG SAFETY OFFICE REVIEWER

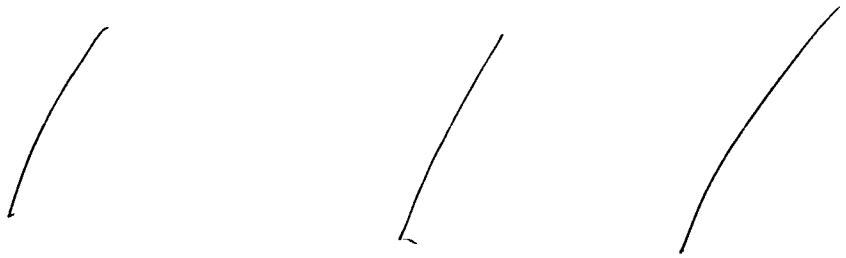
Carol Holquist
11/30/2006 02:15:25 PM
DRUG SAFETY OFFICE REVIEWER

From: Dempsey, Mary
Sent: Tuesday, November 14, 2006 10:07 AM
To: Curtis, Felecia
Cc: Karwoski, Claudia B; Dempsey, Mary
Subject: Lisdexamfetamine (NDA 21-977)

Hi Felecia,

OSE has reviewed the New River Pharmaceuticals' response to your Lisdexamfetamine AE letter and we have the following comment.

We note the Sponsor's response dated October 24, 2006 to the Agency's comments on the RMP in the AE letter dated October 6, 2006. We additionally request that the Sponsor



Felecia, please let me know if you have any questions.
Thanks,
MaryD

Mary Dempsey
Risk Management Program Coordinator
Office of Surveillance & Epidemiology (OSE)
FDA/CDER
301-796-0147

10903 New Hampshire Avenue
CDER Building #22, Room 4326
Silver Spring, MD 20993
New Email Address: Mary.Dempsey@fda.hhs.gov

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: November 9, 2006

To: Thomas Laughren, M.D., Director
Division of Psychiatry Products (HFD-130)

Through: Michael Klein, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff (HFD-009)

Subject: Consultation on draft labeling for
NRP104 (lisdexamfetamine)
NDA 21-977
Indication: treatment of ADHD
Sponsor: New River Pharmaceuticals, Inc.

Background:

CSS was consulted by HFD-130 regarding the Sponsor's redrafting of the abuse liability related sections of the FDA-proposed label for lisdexamfetamine, which were previously written by CSS. The following CSS comments address each of the Sponsor's proposed changes in the label.

Conclusions and Recommendations

[redacted]

3 Page(s) Withheld

Trade Secret / Confidential

✓ Draft Labeling

Deliberative Process

Withheld Track Number: Administrative/Correspondence-2

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/s/

Katherine Bonson
11/9/2006 04:58:54 PM
PHARMACOLOGIST

Michael Klein
11/9/2006 05:12:39 PM
CHEMIST

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 25, 2006

TO: Thomas Laughren, M.D., Director
Division of Psychiatric Products, HFD-120

THROUGH: Gerald Dal Pan, M.D., M.H.S, Director
Office of Surveillance and Epidemiology (OSE), HFD-400

FROM: OSE Lisdexamfetamine Risk Management Program Review Team

DRUG: Lisdexamfetamine Mesylate

NDA: 21-977

APPLICANT: New River Pharmaceuticals, Inc.
Shire Development Inc.

SUBJECT: Risk Management Program, submitted June 9, 2006

PID: D060507

1 EXECUTIVE SUMMARY

This consult follows a request from the Division of Psychiatric Products (DPP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the Risk Management (RMP) for lisdexamfetamine mesylate, as treatment for Attention Deficit Hyperactivity Disorder (ADHD).

Lisdexamfetamine is an inactive prodrug which is metabolized to active dextroamphetamine. The Sponsor has submitted an RMP because of the potential abuse, diversion, and misuse of amphetamine products. However, the Sponsor believes that this product may be less attractive to abusers because injecting or snorting lisdexamfetamine bypasses gastrointestinal metabolism; metabolism is required for release of the active amphetamine. [redacted]. 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).

The sponsor has proposed to address the issue of abuse and diversion with a risk management program that focuses on surveillance and education. If the product is approved as a Schedule II product, we believe the Sponsor's proposed RMP, which is consistent with the recently approved Daytrana[1], is sufficient. [redacted]

2 BACKGROUND

Lisdexamfetamine dimesylate (prodrug of d-amphetatmine) is an NME and in its intact form lacks stimulant properties and is pharmacologically inactive. When taken orally, the amide linkage is hydrolyzed in the gastrointestinal tract, releasing active d-amphetamine. The sponsor is seeking approval for the treatment of children (ages 6-12) with attention deficit hyperactivity disorder (ADHD) with a dosing regimen of 30 to 70 mg/day.

The Medical Officer's (MO) review of the safety data revealed safety findings consistent with the previously observed safety profile of amphetamines. The stimulant ADHD products have been associated with several major safety issues including cardiovascular events (sudden death with structural cardiac abnormalities or other serious heart problems, hypertension, tachycardia), psychiatric events (psychotic symptoms, manic symptoms, aggressive behavior or hostility), long-term suppression of growth, seizures, and visual disturbance. [2]

The cardiovascular safety concerns (including sudden death, hypertension, and tachycardia) were the subject of two advisory committee meetings earlier this year. The Drug Safety and Risk Management (DSaRM) Advisory Committee (AC) met on February 9, 2006 to discuss how best to assess the cardiovascular risk. The DSaRM AC recommended that all stimulant ADHD drugs carry a boxed warning. The Pediatric Advisory Committee met on March 22, 2006 to discuss the neuropsychiatric and cardiovascular adverse events related to ADHD medications. Based upon the discussion and recommendations made by the members of the two different advisory committees, the Agency requested labeling changes in order to adequately warn practitioners and patients about the use of CNS stimulant products to treat ADHD. These labeling changes are included in appendix 1.

The Sponsor has submitted a Risk Management Plan (RMP) because of the potential abuse, diversion, and misuse of amphetamine products. In their RMP submission the Sponsor asserts that lisdexamfetamine would be less attractive to abusers or diverters than currently marketed amphetamines because oral administration requires rate limiting metabolism for amphetamine to be released. Abuse of lisdexamfetamine by injection and snorting is also felt by the Sponsor to be less attractive to abusers because both methods

[1] Daytrana (methylphenidate transdermal system) is an adhesive-based matrix transdermal system (patch) that is applied to intact skin.

[2] Michelle Chuen, M.D., Clinical Review of NDA 21-977 Lisdexamfetamine Dimesylate, July 28, 2006.

bypass the liver, reducing or eliminating its euphoric effects. They also stated that taking excessive amounts orally will overwhelm the metabolic transformation resulting in a peak concentration curve and that additional amounts will not result in higher levels of bioavailable amphetamine.[3] [redacted].

The Controlled Substance Staff (CSS) has recommended that lisdexamfetamine be placed into Schedule II of the Controlled Substances Act (CSA) based on their review of the abuse potential in human and preclinical studies.[4] The final CSA Schedule of this drug is yet to be determined by the Drug Enforcement Agency (DEA). With the exception of Modafinil (Schedule IV under CSA) all other stimulant products approved for ADHD are Schedule II under the CSA.

3 SUMMARY OF PROPOSED RISK MANAGEMENT PLAN

The Sponsor proposes several components of the risk management plan with the intent of reducing and detecting abuse and diversion.

3.1 PROPOSED RISKMAP

[redacted]

[3] NRP 104 Risk Management Program, NDA 21-977, Vol 1, Mod 1, 1.16, pg 3.
[4] Katherine Bonson, Ph.D., Abuse liability of NRP104 (Lisdexamfetamine dimesylate) NDA 21-977; in DFS, dated September 12, 2006.

3 Page(s) Withheld

✓ Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Administrative/Correspondence-3

OSE Lisdexamfetamine Risk Management Program Review Team

Nancy Clark, PharmD., BCPP, Regulatory Project Manager, DSRCS
Mary Dempsey, Project Management Officer, OSE-IO
Catherine Dormitzer, PhD, Epidemiologist, DDRE
Jodi Duckhorn, MA, Team Leader Patient Information and Research, DSRCS
Oluchi Elekwachi, PharmD., Safety Evaluator, DDRE
Claudia B. Karwoski, Pharm.D., Scientific Coordinator for Risk Management, OSE-IO
Alina R. Mahmud, R.Ph. Team Leader, DMETS
Marilyn Pitts, Pharm.D, Team Leader Safety Evaluator, DDRE
Joyce Weaver, Pharm.D., Senior Drug Risk Management Analyst, OSE-IO
Mary Willy, Ph.D., Senior Drug Risk Management Analyst, OSE-IO (detail)

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/s/

Mary Dempsey
9/25/2006 02:42:08 PM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
9/25/2006 02:50:44 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: September 12, 2006

To: Thomas Laughren, M.D., Director
Division of Psychiatry Drug Products (HFD-130)

Through: Deborah B. Leiderman, M.D., Director
Michael Klein, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff (HFD-009)

Subject: Abuse Liability of NRP-104 (Lisdexamfetamine dimesylate; L-lysine-d-amphetamine dimethanesulfonate)
Labeling Recommendations
NDA 21-977
Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor: New River Pharmaceuticals, Inc.

I. Summary:

This CSS consult evaluates the abuse liability of lisdexamfetamine dimesylate (NDA 21-977), as requested by the Division of Psychiatry Products (HFD-130), to help determine appropriate labeling and scheduling of the drug. Lisdexamfetamine is a prodrug of d-amphetamine, a Schedule II drug with known high abuse liability. Thus, the label for lisdexamfetamine should reflect its high liability for abuse. Additionally, CSS has prepared an Eight Factor Analysis on behalf of the Department of Health and Human Services (HHS) recommending that lisdexamfetamine be placed into Schedule II of the Controlled Substances Act (CSA). The CDER/CSS recommendation for scheduling must be cleared through the CDER Director, the FDA Office of the Commissioner, the Office of Chief Counsel and finally by the Assistant Secretary for Health at HHS prior to transmittal to the Drug Enforcement Administration (DEA).

The final scheduling of this drug under the CSA is currently proceeding, but is not yet complete. The Sponsor has made the commitment not to market this drug until the scheduling is finalized by the DEA, pursuant to 21 USC 811 and 812. As such, an approvable letter should include a statement that the drug cannot be marketed until scheduling is complete, and that approval of the final printed labeling is contingent upon a final scheduling action by the DEA.

II. Background:

NRP-104 (lisdexamfetamine dimesylate) is proposed for the treatment of attention deficit hyperactivity disorder (ADHD), at a recommended therapeutic daily dose of 30, 50 or 70 mg. In this document, *lisdexamfetamine*, the free base of NRP-104, will be used to refer to the drug. A trade name for lisdexamfetamine has not yet been selected. Lisdexamfetamine is not currently marketed in any country.

Lisdexamfetamine is a new molecular entity that consists of d-amphetamine covalently bound to the amino acid L-lysine. Upon oral ingestion, lysine is cleaved in the gastrointestinal system to produce free d-amphetamine. Thus, d-amphetamine, the ultimate therapeutic compound resulting from lisdexamfetamine, is a Schedule II drug with a known high abuse liability. All products containing d-amphetamine, including extended-release formulations, are in Schedule II of the CSA.

On October 31, 2003, the DEA advised the Sponsor that lisdexamfetamine was not currently considered a scheduled substance, but could be scheduled under the CSA if a review of its abuse and dependence liabilities warranted a scheduling action. [redacted]. However, based on a review of the data submitted, CSS is recommending that lisdexamfetamine be controlled under Schedule II.

III. Conclusions

Conclusions from the evaluation of the lisdexamfetamine abuse liability studies submitted in the NDA (clinical data, pharmacokinetics, physical dependence and tolerance, preclinical data and chemistry/pharmacology data) are summarized below:

1. Lisdexamfetamine has a pharmacokinetics/pharmacodynamic profile similar to that of d-amphetamine, in extended- or sustained-release d-amphetamine products, which are all in Schedule II of the CSA.
2. Adverse events (AEs), including euphoria, observed in clinical trials with lisdexamfetamine are consistent with those produced by d-amphetamine.
3. Lisdexamfetamine produced rewarding effects that are similar to those produced by d-amphetamine, in subjects with a history of substance abuse, following administration in a human pharmacology abuse liability study.
4. Lisdexamfetamine produced psychological dependence and tolerance upon repeated administration, as has been observed d-amphetamine abusers.
5. In animal behavioral studies, lisdexamfetamine produced pharmacodynamic effects indicative of abuse liability similar to those of Schedule II stimulants, including d-amphetamine and cocaine.
6. [redacted]

IV. Summary of Data and Findings from Abuse Liability Studies

The following is a summary of the data and findings from the lisdexamfetamine abuse liability studies submitted in the NDA that form the basis of CSS recommendations for the abuse-related sections of the label, as found in Section V.

Clinical Data

* Adverse events (AEs) produced by lisdexamfetamine are consistent with those produced by d-amphetamine. In Phase 2/3 clinical trials with children diagnosed with ADHD, AEs included affect lability, irritability, insomnia, nervousness, anorexia, weight loss, increase in blood pressure, tachycardia and palpitations. These AEs are similar to those found in the drug labels for Adderall (a Schedule II drug product containing immediate-release and extended-release d-amphetamine) and Dexedrine (a Schedule II drug product containing immediate-release and sustained-release d-amphetamine).

* Euphoria was observed in clinical trials with lisdexamfetamine. The central nervous system AE profile of lisdexamfetamine reported in Phase 1 clinical trials for lisdexamfetamine included serious psychiatric symptoms such as 11% euphoria in healthy adults and 11% mood alterations in healthy children.

* Lisdexamfetamine produced rewarding effects in subjects with a history of substance abuse following oral administration in a human laboratory abuse liability study. Orally administered lisdexamfetamine (150 mg) produced statistically significant increases in measures of drug liking compared to placebo. Drug liking was evaluated by a standard battery of subjective measures, using doses up to slightly more than twice that of the highest recommended therapeutic dose of 70 mg. These data also showed that the positive rewarding effects of 150 mg lisdexamfetamine were statistically indistinguishable from those produced by 40 mg d-amphetamine, a Schedule II drug.

* Lisdexamfetamine produces rewarding effects when administered intravenously. In a human laboratory abuse liability study in which lisdexamfetamine was administered by intravenous infusion, 50 mg lisdexamfetamine produced positive subjective responses that were greater than placebo but less than those produced by 20 mg intravenous d-amphetamine. Higher doses of lisdexamfetamine were not tested. Data from this human study are consistent with animal data showing that monkeys self-administer lisdexamfetamine via intravenous infusion.

Pharmacokinetics

* The total d-amphetamine exposure (AUC) resulting from 75 mg lisdexamfetamine is equivalent to that produced by 30 mg Dexedrine (a Schedule II immediate-release d-amphetamine drug).

* Similar plasma curves for peak and duration (AUC for 24 hr) for d-amphetamine are produced by 75 mg lisdexamfetamine and 35 mg Adderall XR (a Schedule II extended-release d-amphetamine drug).

* Peak plasma levels (Cmax) of d-amphetamine resulting from 50 and 70 mg lisdexamfetamine correspond respectively to those produced by 30 and 50 mg immediate-release d-amphetamine (a Schedule II drug).

* The pharmacokinetics of lisdexamfetamine, as measured by plasma d-amphetamine, becomes non-linear in humans at doses between 130 and 150 mg. Thus, plasma d-amphetamine levels continue to increase, but at a rate less than that observed with lower doses.

Physical Dependence and Tolerance

* Lisdexamfetamine may produce physical and psychological dependence. Physical dependence, withdrawal and psychological dependence were not directly assessed in either animals or humans. However, lisdexamfetamine metabolizes to d-amphetamine, a Schedule II drug known to produce a withdrawal syndrome. Additionally, there is evidence that lisdexamfetamine produces rewarding effects that are similar to those produced by d-amphetamine, suggesting an equivalent liability in producing psychological dependence.

* Lisdexamfetamine produced tolerance upon repeated administration. The development of tolerance was demonstrated in that eighty percent of subjects in clinical trials needed to increase their dose during the study. This could be expected, given that lisdexamfetamine metabolizes to d-amphetamine, which is well-known to produce tolerance in drug abusers

Preclinical Data

* In animal behavioral studies, lisdexamfetamine produced pharmacodynamic effects indicative of abuse liability similar to those of Schedule II stimulants, including d-amphetamine and cocaine. Lisdexamfetamine was self-administered via intravenous infusion by monkeys trained to self-administer the Schedule II stimulant, cocaine. In drug discrimination tests in monkeys, intragastric lisdexamfetamine produced full generalization to the interoceptive cue produced by intragastric d-amphetamine.

* Locomotor tests in rodents showed that lisdexamfetamine produces stimulant effects similar to those of d-amphetamine (a Schedule II drug) when the drugs were administered intravenously, intranasally and orally.

Chemistry and Pharmacology Data

* Lisdexamfetamine does not bind to CNS sites, but its major active metabolite, d-amphetamine, a Schedule II drug with high abuse liability, acts directly on monoamine transporters to produce rewarding effects. Other substances that act as prodrugs for d-amphetamine, including

fenethylline, ethylamphetamine and dimethylamphetamine, are Schedule I drugs with high abuse liability.

[redacted]

V. Label Review

CSS has reviewed the label text proposed by the Sponsor and recommends extensive revisions, based on our evaluation of the abuse liability data submitted in the NDA (see section III). In addition, CSS recommends that the lisdexamfetamine label be consistent with the labels of other d-amphetamine-containing products and ADHD drugs currently marketed.

Below is a proposed revised label text, as it relates to abuse liability:

4 Page(s) Withheld

Trade Secret / Confidential

✓ Draft Labeling

Deliberative Process

Withheld Track Number: Administrative/Correspondence-4

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

/s/

Katherine Bonson
9/12/2006 03:27:25 PM
PHARMACOLOGIST

Michael Klein
9/12/2006 03:45:07 PM
CHEMIST

Deborah Leiderman
9/12/2006 06:30:41 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 24, 2006

TO: Susan Player, Regulatory Project Manager
Michelle Chuen, M.D., Medical Officer
Thomas P. Laughren, M.D., Director
Division of Psychiatry Products, HFD-130

THROUGH: Constance Lewin, M.D., M.P.H., Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Jose Javier Tavarez, M.S.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-977

SPONSOR: New River Pharmaceuticals

DRUG: Lisdexamfetamine dimesylate

CHEMICAL CLASSIFICATION: Type 1

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Attention Deficit Hyperactivity Disorder (ADHD)

CONSULTATION REQUEST DATE: February 3, 2006

PDUFA GOAL DATE: October 6, 2006

I. BACKGROUND

Clinical investigator inspections were conducted at three clinical sites that performed studies for which the sponsor submitted data in NDA 21-977. In addition, a sponsor-monitor inspection was requested because the investigational drug is a new molecular entity (NME) product intended for

treatment of Attention Deficit Hyperactivity Disorder. The clinical investigator inspections were conducted according to the Compliance Program 7348.811, the Inspection Program for Clinical Investigators. The inspections covered work performed under protocols NRP104.201 and NRP104.301.

In this NDA, the sponsor has included results of protocols NRP104.201 and NRP104.301. Protocol NRP104.201 was a phase 2, randomized, multi-center, double-blind, 3-treatment and 3-period crossover study conducted in a school laboratory environment to evaluate efficacy and safety of NRP104 (30 mg, 50 mg, or 70 mg) and Adderall XR® compared with placebo in treatment of children with Attention-Deficit Hyperactivity Disorder (ADHD).

Protocol NRP104.301 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group study of 4-week duration of the efficacy and safety with three daily doses of NRP104 compared to placebo in children aged 6 to 12 years with ADHD.

For protocol NRP104.301, the primary efficacy endpoint was the change from baseline of the ADHD-Rating Scale at the treatment endpoint. For protocol NRP104.201, the primary efficacy endpoint was the average of Swanson, Kotkin, Agler, M. Flynn and Pelham rating scale (SKAMP) across the treatment assessment day.

Basis for Sites Selection: The sponsor and three clinical sites were inspected: Drs. Childress, [redacted], and Lopez's sites. These sites covered a relatively large percentage of subject population for both protocols NRP104.201 and NRP104.301. The goals of inspection included validation of submitted data and compliance of study activities with FDA regulations. Among the elements reviewed for compliance were subject record accuracy, informed consent, protocol inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of adverse events.

II. RESULTS (by site):

Clinical Investigator	Location	Protocol(s)	Inspection Date	EIR Received Date	Final Classification
Dr. Ann Childress	Center for Psychiatry and Behavioral Medicine, Inc. Las Vegas, NV	104.201 104.301	3/7-24/2006	4/5/2006	VAI
[redacted]	[redacted]	104.301	4/25 – 5/3/2006	5/26/2006	VAI
Dr. Frank Lopez	Children's Developmental Center P.A. Maitland, Florida	104.201 104.301	5/30 – 6/13/2006	7/19/2006	VAI
Sponsor					
New River Pharmaceuticals	1881 Grove Avenue Radford, VA	104.201 104.301	4/11-19/2006	5/8/2006	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviation(s) from regulations. Data acceptable
OAI = Significant deviations from regulations. Data unreliable
Pending = Inspection not completed

(1) Dr. Ann Childress, M.D.
Center for Psychiatry and
Behavioral Medicine, Inc.
7351 Prairie Falcon Road
Las Vegas, Nevada 89128

a. What was inspected?

The FDA field investigator reviewed the records for all 11 and 4 subjects enrolled in the protocols NRP104.201 and NRP104.301, respectively. The case report forms (CRFs) were examined and compared to source documents. The FDA investigator reviewed the source documents, CRFs and compared with data listing provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

b. Limitations of inspection: None.

c. General observations/commentary:

Inspection revealed protocol deviations. Significant findings are detailed below.

Study NRP104.201

According to the protocol, subjects were to be followed up with a telephone call approximately 30 days after the last dose of study medication. This protocol requirement was not conducted for the following subjects:

1) Subject #002 was administered the last dose of study medication on 11/27/2004; however, the follow-up phone call was not made until 2/8/2005.

2) Subject #010 was administered the last dose of study medication on 11/27/2004; however, there is no documentation that follow up data were collected approximately 30 days after the last dose of study medication.

Study NRP104.301

The protocol required that subjects have a hematology test at screening. However, a hematology test was not performed for subject #305 at screening.

There were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms.

Recommendation: Data from this clinical site appear acceptable for use in support of this NDA.

(2) [redacted]

a. What was inspected?

The FDA field investigator reviewed the records for all 18 subjects enrolled in the protocol NRP104.301. The case report forms (CRFs) were examined and compared to source documents. The FDA investigator reviewed the source documents, CRFs and compared with data listing provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

b. Limitations of inspection: None.

c. General observations/commentary

Inspection revealed protocol deviations and unreported adverse events. Significant findings are detailed below.

Study NRP104.301

1) The protocol amendment 1 dated 10/8/2004 required that a minimum of three electrocardiograms (taken at least 10 minutes apart) were to be collected at screening visit. The inspection revealed that electrocardiograms were collected less than 10 minutes apart for subjects 306, 307, 308, 309, 310, 311, 313, 314, 315, 316, 317, and 318.

2) The protocol specified that a hematology test was to be performed at screening. The protocol required that potential subjects be excluded from the study if they had any clinically significant laboratory abnormalities at screening. Subject 318 was enrolled in the study; however, the protocol-required screening hematology test was not performed.

3. The physician progress note dated 12/23/2004 reports the adverse event "more emotional overall" for subject 306; however, the adverse event was not reported to the sponsor.

4. The physician progress note dated 2/14/2005 reports the adverse event "stomach ache" for subject 319; however, the adverse event was not reported to the sponsor.

Recommendation: Data from this clinical site appear acceptable for use in support of this NDA supplement.

(3) **Frank Lopez, M.D.**
1992 Mizell Avenue
Winter Park, FL 32792

a. What was inspected?

The FDA field investigator reviewed the records for 10 of the 18 subjects enrolled in the protocol NRP104.201. The field investigator also reviewed the records for 13 of the 24 subjects enrolled in the protocol NRP104.301. The case report forms (CRFs) were examined and compared to source documents. The FDA field investigator reviewed the source documents, CRFs and compared with data listing provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

b. Limitations of inspection: None.

c. General observations/commentary

Inspection revealed protocol deviations, unreported adverse events, and inaccurate case histories. Significant findings are detailed below.

Study NRP104.201

According to the protocol, adverse events (AEs) were to be recorded in the case report form regardless of treatment group or suspected relationship to study drug. The following AEs were not documented in the case report form as required by the protocol:

1) The Master Adverse Events Worksheet dated 11/21/2004 for subject 04-006 recorded that the subject experienced insomnia and decreased appetite; however, these AEs were not documented in the case report form.

2) The Master Adverse Events Worksheet dated 11/21/2004 for subject 04-014 recorded that the subject experienced insomnia, decreased appetite,

and stomach ache; however, these AEs were not documented in the case report form.

The Master Adverse Events Worksheet documented that these AEs were probably related to study drug.

Study NRP104.301

The following information in case report forms (CRFs) does not accurately represent source data for pertinent study-related values:

1) For subject 04-322, the Conner's Parent Rating Scale (CPRS) Worksheet for visit 3 reported a score of 1 for item #26. However, the case report form documented a score of 2 for item #26.

2) For subject 04-323, the CPRS Worksheet for visit 2 reported the following scores that were inconsistent with the scoring reported in the CRF:

CPRS Worksheet	CRF
item #19 – score of 3	Item #19 – score of 1
item #20 – score of 2	Item #20 – score of 3
item #21 – score of 3	Item #21 – score of 1

Recommendation: Data from this clinical site appear acceptable for use in support of this NDA supplement.

(4) Randal J. Kirk, M.S.
Chairman, CEO and President
New River Pharmaceuticals
1881 Grove Avenue
Radford, VA 24141

a. What was inspected?

The sponsor-monitor inspection was requested because the investigational drug is a new molecular entity. The inspection was conducted in accordance with the Sponsor/Monitor/Contract Research Organization (CRO) compliance program. The inspection audited protocols NRP104.201, and NRP104.301. For protocol NRP104.201, four clinical sites were reviewed. Forty clinical sites were reviewed for protocol NRP104.301. Dr. Frank Lopez, Dr. Ann Childress, and Dr. [redacted] were among the clinical investigators reviewed.

The inspection reviewed the following: quality assurance and clinical operations, study monitoring procedures, records and reports, participating clinical investigators, monitoring reports, CRFs, data collection, and study drug accountability. The FDA investigator also compared selected subject CRFs and

were compared with the firm's data listings.

b. Limitations of inspection: None.

c. General observations/commentary

There were no significant inspectional findings that would adversely impact data acceptability.

Recommendation: The study appears to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As stated above, there were instances of protocol deviations at the three clinical investigator sites inspected. The review division should note the unreported adverse events noted above for Drs. [redacted] and Lopez's sites. In general, for the three clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. Overall, data generated for protocols NRP104.201 and NRP104.301 at these clinical sites appear acceptable for use in support of NDA 21-977.

{See appended electronic signature page}

Jose Javier Tavarez, M.S.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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

/s/

Jose Tavarezpagan
9/1/2006 11:43:04 AM
UNKNOWN

Constance Lewin
9/1/2006 12:30:04 PM
MEDICAL OFFICER

CSS teleconference Meeting Minutes
NRP104, NDA 21,977
August 10, 2006
2:00 - 2:30 pm

Attendees:

New River Pharmaceuticals:	Suma Krishnan, MS, Vice President, Product Development
	[redacted], MD, Clinical Consultant
	Annie Foster, Associate Manager, Regulatory Affairs
FDA:	Thomas Laughren, M.D, Acting Division Director
	Thomas Oliver, Ph.D Chemistry Team Leader
	Barr Rosloff, Ph.D, Pharmacology/Toxicology Supervisor
	Michelle Chuen, M.D, Clinical Reviewer
	Lyudmila Soldatova, Chemistry Reviewer
	Katherine Bonson, Ph.D, Pharmacologist, Controlled substance Staff (CSS)
	Michael Klein, Ph.D- Team Leader, CSS
	Felecia Curtis, Regulatory Project Manager
	Susan Player, Regulatory Project Manager
	James Hunter, R.Ph., MPH, Senior Project Manager, CSS

The purpose of the meeting was to discuss abuse liability issues related to NDA 21-977, lisdexamfetamine dimesylate. The sponsor was supplied a list of the three questions from the Controlled Substance Staff (CSS) one day prior to the telecon. NRP confirmed receipt of these questions.

CSS Comments:

Study NRP104.A02 (Module 5, Sequence 1. Volume 60)

1) According to Abreu et al., 2000, the infusion rate of intravenously-administered drugs of abuse can greatly influence the subjective positive response to a drug. In the human laboratory abuse liability study using intravenous administration of lisdexamphetamine (Study NRP104.A02), what was the infusion rate for both amphetamine and for lisdexamphetamine?

NRP's Response:
1. An intracatheter was used on all subjects and replaced every three days.
2. NRP104 (lisdexamfetamine dimesylate), d-amphetamine and placebo were all injected in blinded manner via syringe over a one minute timed period.
3. Administration of study drug was always timed using a stop watch and monitored by a physician. The first blood draw was taken five minutes after dosing.

The Agency did not request further clarification.

Study CA04-NRP104 (Module 5. Sequence 1. Volume 77)

[redacted]

[redacted]

Clarification of NRP-I 04 Abuse Liability Issues

3) CSS would like to request a face-to-face meeting with the Sponsor and the Division on August 25, 2006, to clarify the Sponsor's position regarding the scheduling placement of lisdexamphetamine under the Controlled Substances Act.

NRP's Response:
NRP is available for a face to face meeting on the above requested date. An exact date and time will be determined by the Agency.

The teleconference ended.

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/s/

James Hunter
8/22/2006 03:42:21 PM
CSO

Michael Klein
8/23/2006 10:19:46 AM
CHEMIST

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-977 Supplement # 0 Efficacy Supplement Type SE- N/A

Proprietary Name:
Established Name: Lisdexamfetamine dimesylate
Strengths: 30 mg, 50 mg, 70 mg

Applicant: New River Pharmaceuticals, Inc.
Agent for Applicant (if applicable): N/A

Date of Application: December 6, 2005
Date of Receipt: December 6, 2006
Date clock started after UN: N/A
Date of Filing Meeting: 1/24/06
Filing Date: 2/4/06
Action Goal Date (optional): User Fee Goal Date: 10/6/06

Indication(s) requested: Treatment of attention deficit hyperactivity disorder

Type of Original NDA: (b)(1) X (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 X 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 X NO ☐

User Fee Status: Paid X 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 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 X
  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 X

- 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 X
  If yes, explain:

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

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

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

- Submission complete as required under 21 CFR 314.50? YES X 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 X
   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 X 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?
   Proposed Labeling

   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 X NO ☐

- Exclusivity requested? YES, 5 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 X 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 X

- 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 X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X 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 X NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES X 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.

- List referenced IND numbers: 67482

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

- End-of-Phase 2 Meeting(s)? Date(s) 7/29/04 NO ☐
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 7/6/05 NO ☐
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO X
  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 X 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 X
  NDA submitted before 6/30/06
  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: No waiver requested.

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A X YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A X YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☐ YES X 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 X NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X 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 X

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

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/24/06

NDA #: 21-977
DRUG NAMES: Lisdexamfetamine dimesylate (NRP104)

APPLICANT: New River Pharmaceuticals, Inc.

BACKGROUND: New Molecular Entity

ATTENDEES: Richardae Araojo, Susan Player, Tom Oliver, Tom Laughren, Paul Andreason, Lyudmila Soldatova, Ray Baweja, Andre Jackson, Javier Tavarez, Barry Rosloff, Ikram Elayan, Peiling Yang, Yeh-Fong Chen, Michelle Chuen

ASSIGNED REVIEWERS (including those not present at filing meeting) : See attendees; James Hunter and Katherine Bonson did not attend filing meeting.

Discipline/Organization	**Reviewer**
Medical:	Michelle Chuen
Secondary Medical:	
Statistical:	Yeh-Fong Chen
Pharmacology:	Ikram Elayan
Statistical Pharmacology:	
Chemistry:	Lyudmila Soldatova
Environmental Assessment (if needed):	
Biopharmaceutical:	Andre Jackson
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Javier Tavarez
OPS:	
Regulatory Project Management:	Susan Player
Other Consults:	

Per reviewers, are all parts in English or English translation? YES X NO ☐
If no, explain:

CLINICAL FILE X REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES X NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO X

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A X YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A	X	FILE	☐	REFUSE TO FILE	☐
STATISTICS	N/A	☐	FILE	X	REFUSE TO FILE	☐
BIOPHARMACEUTICS			FILE	X	REFUSE TO FILE	☐

- Biopharm. study site audits(s) needed? ☐ NO X
  YES

PHARMACOLOGY/TOX	N/A	☐	FILE	X	REFUSE TO FILE	☐

- GLP audit needed? YES ☐ NO X

CHEMISTRY			FILE	X	REFUSE TO FILE	☐

- Establishment(s) ready for inspection? YES X NO ☐
- Sterile product? YES ☐ NO X
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

X 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.X Convey document filing issues/no filing issues to applicant by Day 74.

Susan E. Player
Regulatory Project Manager
Version 6/14/2006

Appears This Way
On Original

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/s/

Susan Player
8/10/2006 01:33:06 PM
CSO

Delayed entry

Steve Hardeman
8/10/2006 01:41:05 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE/IO
Attention: Mary Dempsey

FROM:
Division of Psychiatry Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 22, 2006		21-977	NDA amendment of proposed Risk Management Plan	June 9, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
NRP104 (lidexamfetamine)		Treatment of ADHD	**September 6, 2006**

NAME OF FIRM: New River Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

COMMENTS/SPECIAL INSTRUCTIONS: **The sponsor has submitted a proposed RMP. Please review for adequacy and provide comments to DPP review team and sponsor.**
Thank you!

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Susan E. Player, MS, APRN, BC Regulatory Project Manager CDER/ODEI/DPP, HFD-130 White Oak Building 22, Room 4392 Ph. 301-796-1074 E-mail: susan.player@fda.hhs.gov	☐ MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Thomas Laughren
6/23/2006 08:42:24 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*: CDER/OCTAP/DPDD/HFD-960 Attention: Grace Carmouze	FROM: HFD-130/Division of Psychiatry Products

DATE May 8, 2006	IND NO.	NDA NO. 21-977	TYPE OF DOCUMENT New Chemical Entity NDA	DATE OF DOCUMENT December 6, 2005

NAME OF DRUG NRP104 (Lisdexamfetamine dimesylate)	PRIORITY CONSIDERATION **High**	CLASSIFICATION OF DRUG ADHD	DESIRED COMPLETION DATE **June 7, 2006**

NAME OF FIRM: New River Pharmaceuticals

REASON FOR REQUEST

COMMENTS/SPECIAL INSTRUCTIONS:

The Division of Psychiatry Products is currently reviewing NDA 21-977 (lisdexamfetamine dimesylate capsules for ADHD). The study population consisted of male and female patients between the ages of 6 and 12, inclusive, and we would like to provide the sponsor some guidance regarding potentially clinically important values (i.e., outlier criteria) regarding laboratory tests (chemistry, hematology, and urinalysis), vital signs (SBP, DBP, P, and body temperature), and ECG's (HR, QT, QTc, PR interval, and QRS interval). Attached please find relevant information from the sponsor's submissions. What are reasonable outlier criteria in the study population (male and female subjects aged 6 to 12) for the laboratory values, vital signs, and ECG measurements listed above?

Thanks!

SIGNATURE OF REQUESTER Susan E. Player Regulatory Project Manager 301-796-1074 Susan.player@fda.hhs.gov	METHOD OF DELIVERY (Check one) MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Thomas Laughren
5/10/2006 01:19:51 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
New River Pharmaceuticals Inc.
1861 Pratt Drive
Suite 1090
Blacksburg, VA 24060

2. TELEPHONE NUMBER *(Include Area Code)*
(540) 953-0237

3. PRODUCT NAME
NRP104, (2S, 2'S)-2,6-diamino-N-(1-phenylpropan-2-yl)hexanamide dimethanesulfonate

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21,977

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

21, 977
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☒ YES ☐ NO
(See item 8, reverse side if answered YES)

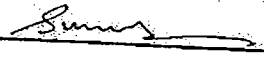
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Vice President, Product Development	12/5/2005

FORM FDA 3397 (12/03)

PSC Media Arts (301) 443-6693 EF

Department of Health and Human Services Public Health Service
Food and Drug Administration
Rockville, MD 20857

NOV 23 2005

Ms. Suma Krishnan
Vice President, Product Development
New River Pharmaceuticals Inc.
1861 Pratt Drive, Suite 1090
Blacksburg, VA 24060

RE: New River Pharmaceuticals Inc., Small Business Waiver Request 2006.018, NDA 21-977, NRP104

Dear Ms. Krishnan:

This responds to your August 15, 2005, letter requesting a waiver of the human drug application fee for new drug application (NDA) 21-977, NRP104 (lisdexamfetamine dimesylate), under the small business waiver provision, section 736(d)(1)(D)[1] of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2006.018). For the reasons described below, the Food and Drug Administration (FDA) grants the New River Pharmaceuticals Inc. (New River) request for a small business waiver of the application fee for NDA 21-977 for NRP104.

According to your letter, New River has — employees and no affiliates. You also state that this application for NRP104 will be New River's first new drug application. You expect to submit the NDA on December 16, 2005.

Under section 736(d)(3) of the Act,[2] a waiver of the application fee is granted to a small business for the first human drug application that it or its affiliate[3] submits to the FDA for review. The small business waiver provision entitles a small business to a waiver when the business meets the following criteria: (1) the business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA's decision to grant New River's request for a small business waiver for its NDA 21-977 for NRP104 is based on the following findings.

(1) The Small Business Administration (SBA) determined and stated in its letter dated October 27, 2005, that New River is affiliated with the following firms: —

[1] 21 U.S.C. 379h(d)(1)(D).
[2] 21 U.S.C. 379h(d)(3).
[3] "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

SBA also noted that New River and its affiliates have fewer than 500 employees.

(2) According to FDA records, the marketing application for NDA 21-977 is the first human drug application, within the meaning of the Act, to be submitted to FDA by New River or its affiliates.[4]

Consequently, your request for a small business waiver of the application fee for NDA 21-977 for NRP104 is granted provided that FDA receives the marketing application for the NDA no later than October 27, 2006, 1 year after the effective date of the size determination made by SBA.

We have notified the FDA Office of Financial Management (OFM) of this waiver decision and have asked them to waive the application fee for New River's NDA 21-977 for NRP104. FDA records show that New River has not yet submitted its NDA 21-977 or the application fee.[5]

If FDA refuses to file the application or New River withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, New River should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions of user fees. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

[4] Although New River is the named applicant for three approved human drug applications, none were initially submitted by New River.

[5] If you have paid the application fee (e.g., our letter and your check crossed in the mail), please contact Dianne Taylor (OFM) at 301-827-0430 to arrange a refund.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 67,482

New River Pharmaceuticals, Inc.
Attention: Suma Krishnan, M.S., M.B.A.
Director, Regulatory Affairs
1861 Pratt Drive, Suite 1090
Blacksburg, VA 24060

Dear Ms. Krishnan:

Please refer to the CMC Pre-NDA meeting between representatives of your firm and FDA on July 6, 2005.

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 Richardae C. Taylor, Pharm.D., Regulatory Health Project Manager, at (301) 594-5793.

Sincerely,
{See appended electronic signature page}

Thomas Oliver, Ph.D.
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING
IND 67,482

Date: July 6, 2005
Time: 11:00 am - 12:00 pm
Drug: NRP 104
Sponsor: New River Pharmaceuticals

Attendees:

Agency

Thomas Oliver, Ph.D.	Chemistry Manufacturing and Controls (CMC) Team Leader
Lyudmila Soldatova, Ph.D.	CMC Reviewer
Richardae Taylor, Pharm.D.	Regulatory Project Manager

Firm

Suma Krishnan, M.S., M.B.A.	Vice President, Product Development
Scott Moncrief, Ph.D.	Senior Scientist, Pre-Clinical
Travis Mickle, Ph.D.	Team Leader, Discovery
—	CMC Consultant
Charles LaPree	Senior Director, Regulatory Affairs, Shire Pharmaceuticals

RE: Pre-NDA Meeting (CMC Only)

Discussion:

The Agency provided specific answers and feedback to the individual questions posed by New River Pharmaceuticals (NRP) and also provided other feedback. The minutes below are organized according to the NRP questions submitted in the briefing package and do not necessarily reflect the order of discussion of the different topics.

Drug Substance

1. Does the Agency agree with the designation of — as starting materials in the synthesis of NRP104?

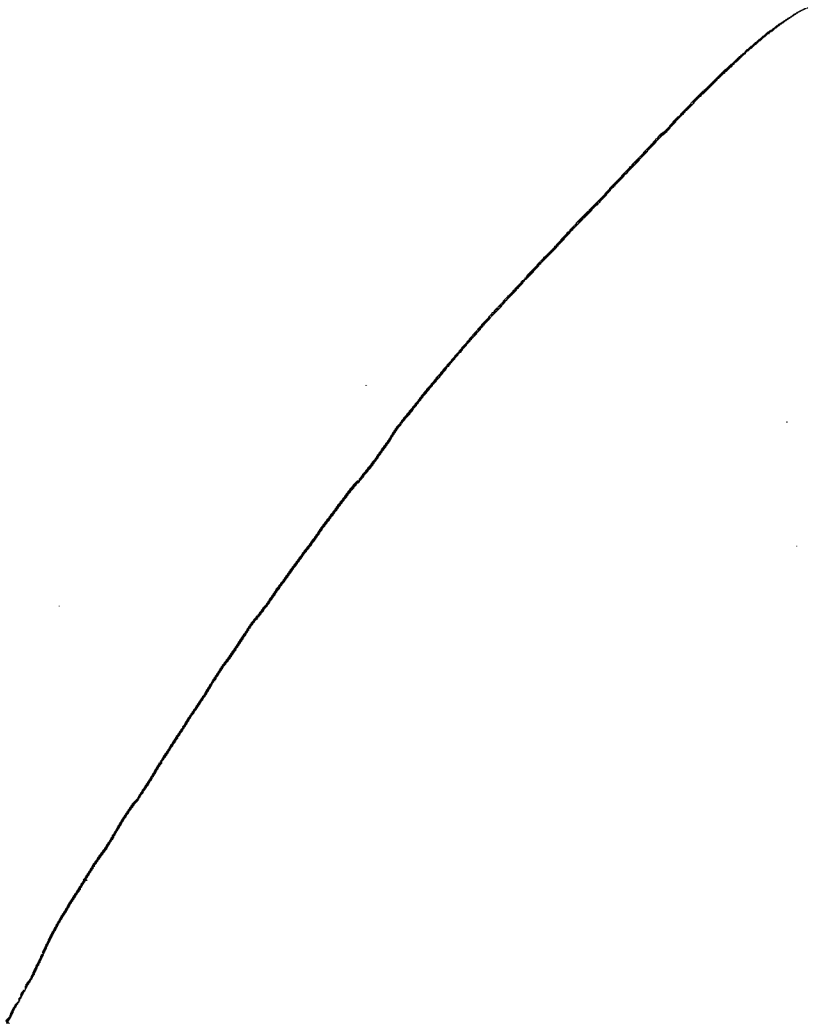
   FDA Response:
   The following comments were provided by the Agency:
   - *is a reasonable starting material; the inclusion of a test for per the proposal in the briefing document is acceptable.*
   - *In the case of the expectation is that CMC information should be provided on how the material is made and received. A DMF for hould be referenced for each intended supplier; if*

there is no reference to a DMF, then the details about the synthesis of [redacted] may be included in the NDA.

- *The specifications for [redacted] should include a [redacted]*
- *The Agency stated that [redacted] can be used. If the sponsor would like the starting material to be [redacted], however, stability data for this material will need to be provided to justify it's selection as a starting material.*

2. Does the Agency concur with the proposed commercial specifications for the drug substance as outlined in Table 4?

FDA Response:
The following comments were provided by the Agency:



E

4 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

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/s/

Thomas Oliver
9/8/2005 07:35:50 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 67,482

New River Pharmaceuticals, Inc.
Attention: Suma Krishnan, M.S., M.B.A.
Director, Regulatory Affairs
1861 Pratt Drive, Suite 1090
Blacksburg, VA 24060

Dear Ms. Krishnan:

Please refer to the Pre-NDA meeting between representatives of your firm and FDA on July 6, 2005.

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 Richardae C. Taylor, Pharm.D., Regulatory Health Project Manager, at (301) 594-5793.

Sincerely,
{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING
IND 67,482

Date: July 6, 2005
Drug: NRP 104
Sponsor: New River Pharmaceuticals

Attendees:

Agency

Thomas Laughren, M.D.	Clinical Team Leader, Acting Division Director HFD-120
Paul Andreason, M.D.	Clinical Team Leader
Roberta Glass, M.D.	Clinical Reviewer
Ikram Elayan, Ph.D.	Pharmacology/Toxicology Reviewer
Barry Rosloff, Ph.D.	Pharmacology/Toxicology Supervisor
Raman Baweja, Ph.D.	Biopharmaceutics Team Leader
Ronald Kavanagh, Ph.D.	Biopharmaceutics Reviewer
Peiling Yang, Ph.D.	Statistical Team Leader
Deborah Leiderman, M.D.	Division Director (HFD-009)
Katherine Bonson, Ph.D.	Pharmacologist (HFD-009)
Richardae Taylor, Pharm.D.	Regulatory Project Manager

Firm

Suma Krishnan, M.S., M.B.A.	Vice President, Product Development
Scott Moncrief, Ph.D.	Senior Scientist, Pre-Clinical
Travis Mickle, Ph.D.	Team Leader, Discovery
[redacted] M.D.	Abuse Liability Consultant
Christopher Lauderback	Senior-Scientist, Chemistry
[redacted]	Clinical Consultant
[redacted]	Pre-Clinical Consultant
[redacted]	Biopharmaceutics Consultant
[redacted]	CMC Consultant
Simon Tulloch	Senior VP, CNS Team Leader
Charles LaPree	Senior Director, Regulatory Affairs, Shire Pharmaceuticals

RE: Pre-NDA Meeting

Discussion:

NONCLINICAL

1. Does the Agency concur that the Scope of the updated Nonclinical Package is adequate to support a New Drug Application on NRP104?

FDA Response: Yes, based on the information presented at this time. The sponsor agreed to provide justification for the use of only females in the supplemental mouse micronucleus assay.

CLINICAL

2. Does the Agency concur that the Scope of the NRP104 Clinical Package is adequate to support a New Drug Application on NRP104?

   FDA Response: Yes, based on the information submitted. However this is a matter of review and will depend on the information submitted at the time of the NDA.

   (See additional comments below from the Office of Clinical Pharmacology and Biopharmaceutics)

3. Does the Agency agree that the proposed approach for the provision of clinical data at the time of NDA filing, supplemented by additional data during the review period as outlined in this document, is acceptable?

   FDA Response: We indicated that their plans for a data package for filing and for a safety update appear to be acceptable. Regarding the safety update, however, we cautioned that we cannot commit to a time frame for reviewing new information submitted during the course of a review, until we have seen the extent of the new information.

4. Does the Agency agree that the proposed ISS and ISE TOC of NDA clinical package are adequate for this NDA?

   FDA Response: Yes, however we have the following additional requests:

   - *A summary of vital signs is needed for all studies*
   - *Include weight in the vital sign assessment*
   - *Ethnicity needs to be broken down more than just by Caucasian and Non- Caucasian*
   - *Provide calculated z-scores (a method utilizing a change based on the number of standard deviations a patient is from their gender/age standardized mean) for all longer term studies.*

   Please see below for comments from the Office of Clinical Pharmacology and Biopharmaceutics.

ABUSE LIABILITY

5. Does the Agency concur that the Scope of the Abuse Liability Package is adequate to support a New Drug Application on NRP104?

   FDA Response: The Abuse Potential Section of the NDA [21 CFR § 314.50 (5) (vii)] should include:

- *Proposal for scheduling and all scientific data that forms the basis of the proposal.*
- *Abuse Potential Assessment:*
    - *Chemistry (including chemical similarity to other drugs of abuse and ability to extract the drug of abuse from the preparation)*
    - *Pharmacokinetics and pharmacodynamics*
    - *Primary data from abuse potential studies in animals and humans*
    - *Adverse events in clinical studies related to abuse potential*
    - *Integrated summaries of safety and efficacy (ISS and ISE)*
    - *Information related to overdose*
    - *Prospective assessment of the incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, diversion during clinical studies.*

6. Does the Agency concur that the Scope of the ——— studies proposed are adequate to support the NDA on NRP104?

   FDA Response: No. CSS conveyed to the Sponsor in January 2005 and April 2005 that

GENERAL

7. Does the Agency have any comments/suggestions on the draft Package Insert provided in Section 10?

   FDA Response: The Division does not usually provide comments regarding labeling before the submission of the NDA, however we noted that the labeling provided did not contain a

8. NRP intends to file a paper NDA in CTD format. Are their any sections of the NDA that the Agency will require to be made available electronically, other than the product labeling? If so, in what format should these be provided?

   FDA Response: We asked that they provide clinical efficacy and pharmacokinetic datasets in electronic form. For the efficacy data, we asked that they include (a) SAS programs that produced all efficacy results, (b) all raw as well as derived variables in .xpt format, (c) SAS programs that produced derived variables from raw variables. We indicated that SAS transport files would be acceptable for the pharmacokinetic data.

9. All references will be appended at the end of each section. Is this acceptable to the Agency?

FDA Response: We asked that they provide all references in one place, separated by discipline, within the NDA submission.

10. NRP has provided a copy of the draft table of contents for the NDA. Is this acceptable to the Agency?

    FDA Response: We asked that they follow available guidance on including adverse events that might be pertinent to abuse liability in the abuse liability section of the application.

Additional discussions during meeting:
New River raised concerns regarding the scheduling of NRP104. New River was applauded for trying to find ways to lower the abuse potential, however at this time CSS would recommend CII scheduling for this drug product based on the regulations. In addition, New River was asked to provide a copy to CSS of their letter from DEA stating that

New River was also asked to provide additional details regarding the metabolism of NRP104.

Additional Requests from the Office of Clinical Pharmacology and Biopharmaceutics:

- Please show doses for both NRP104 and comparator compounds both in terms of actual mass and amphetamine base equivalents. In addition, please show structures and calculations for molecular weights and for amphetamine base equivalents for NRP104, and for both *d*- and *l*- amphetamine from comparator compounds.

- For both pediatric and adult dosages please show values normalized to weight, and body surface area. Pharmacokinetic metrics for normalized dosages should also be provided.

- Please subgroup data by race, ethnicity and gender, (see FDA guidances), and also examine the relationship of age to pharmacokinetics.

- Submission of data sets for phase I and II studies including demographic data, subject numbers, raw concentration and effect vs. time data, and derived pharmacokinetic and pharmacodynamic metrics as SAS transport files would be appreciated. In addition, summary statistics should include mean, standard deviation, coefficient of variation, range, and median.

- The enzymes responsible for cleavage of lysine *in vivo* and the anatomical that produce these enzymes should be ascertained. Reasons include concerns regarding individuals who might exhibit rapid cleavage, dose dumping, and the safety implications for them.

- Based on the results of *in* vitro cleavage studies and physical/chemical considerations, *in vivo* drug and food interaction studies should be conducted as appropriate, e.g. papaya juice and pancreatic enzyme replacements.

-

- Dissolution data should include the raw data for complete profiles in multiple media. Also please note that the dissolution data on batches used in the various clinical studies including phase I, II, and III will be the basis for selecting a specification. Thus complete dissolution profiles for these batches including the raw data should be presented.

-

- Labeling should include information on drug metabolism and elimination.

Post-meeting note:
We also asked that they identify the enzymes responsible for the metabolism of amphetamine and its metabolites and the potential for amphetamine and its metabolites to induce or inhibit drug metabolizing enzymes.

Richardae Taylor, Pharm.D.
Regulatory Project Manager

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/s/

Thomas Laughren
7/21/05 07:38:43 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 67,482

New River Pharmaceuticals, Inc.
Attention: Suma Krishnan, M.S., M.B.A.
Director, Regulatory Affairs
1861 Pratt Drive, Suite 1090
Blacksburg, VA 24060

Dear Ms. Krishnan:

Please refer to the meeting between representatives of your firm and FDA on July 29, 2004. The purpose of this End-of-Phase 2 meeting was to discuss the development of NRP 104 for ADHD.

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 Richardae C. Taylor, Pharm.D., Regulatory Health Project Manager, at (301) 594-5793.

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING
IND 67,482

Date: July 29, 2004
Drug: NRP 104
Sponsor: New River Pharmaceuticals

Attendees:

Agency

Russell Katz, M.D.	Division Director
Paul Andreason, M.D.	Clinical Team Leader
Glenn Mannheim, M.D.	Clinical Reviewer
Fanhui Kong, Ph.D.	Statistical Reviewer
Ronald Kavanaugh, Ph.D.	Biopharmaceutics Reviewer
Thomas Oliver, Ph.D.	Chemistry Team Leader
Lois Freed, Ph.D.	Pharmacology/Toxicology Supervisor
Ikram Elayan, Ph.D.	Pharmacology/Toxicology Reviewer
Jerry Cott, Ph.D.	Pharmacologist (HFD-170)
Richardae Taylor, Pharm.D.	Regulatory Project Manager

Firm

Suma Krishnan, M.S., M.B.A.	Vice President, Product Development
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RE: The purpose of this End-of-Phase 2 Meeting was to discuss the development of NRP 104.

Discussion:

Clinical Biopharmaceutics

1. Does the Division agree with the additional Pharmacokinetic studies proposed in the Briefing Package?

   FDA Response: See comments below from the Office of Clinical Pharmacology and Biopharmaceutics. In addition, the number of SKAMP measurements in NRP201 study should be increased, and we recommend that you obtain blood samples for analysis of d-amphetamine at the same time points.

Comments from the Office of Clinical Pharmacology and Biopharmaceutics:

- *An assessment of relative bioavailability to the optimally available oral formulation, (i.e. a solution or suspension depending on the solubility of NRP104 and ability to make a solution), is needed for NDA submission.*

- *The multiple dose study may be a little short in duration to show the full extent of induction if it occurs. However, the study may not need to be repeated if literature can show that induction is not a concern.*

- *A pediatric PK study is needed. This should be performed prior to phase III studies in order to aid in the selection of dosages for the pivotal phase III studies. Analysis normalized to weight is strongly suggested. Enrollment of subjects should be stratified so that subjects are evenly enrolled over the entire proposed age range of 6 – 12 years old, e.g. subgroup 1: 6 – 7 years old, subgroup 2: 8 – 9 years old, subgroup 3: 10 – 12 years old.*

- *A metabolism and mass balance study is suggested.*

- *The effects of extrinsic factors such as food, and drug-drug interactions should be addressed. The sponsor is advised that the issue of drug-drug interactions may be addressable via literature sources and in vitro data.*

- *The effects of intrinsic factors such as gender, race and weight should also be examined. The effect of these intrinsic factors may be addressed by enrollment of appropriate subjects in various studies and performing subgroup analyses. Use of literature as supportive information may also be appropriate in the present situation.*

- *Complete dissolution profile data in three media and under various conditions should be submitted in the NDA for the pivotal bioavailability study batches and the pivotal clinical efficacy and safety study batches. This information is used for selection of the regulatory method and setting specifications. Data for complete dissolution profiles for stability batches is also useful. In addition dissolution profile data generated for batches used in other human studies is useful for bridging of biopharmaceutic/pharmacokinetic properties. Additional detailed information is available in FDA guidances.*

2. Does the Division concur with the overall design of the two proposed pediatric pivotal Phase 3 studies?

   FDA Response: Yes, include a full range of children aged 6-12.

3. Does the Division concur with the statistical approach and definition of the population to be assessed for efficacy?

FDA Response: New River was told that the Division would be willing to provide comments on their statistical analysis plan. The statistical analysis plan should address how they plan to handle drop-outs and dose response. Also, the Division recommended New River provide a strategy to determine which dose group is most significant.

4. Does the Division agree that the overall clinical development plan represents an adequate safety and efficacy package and ultimately supports registration of the product for the treatment of ADHD in 6-12 year olds?

   FDA Response: Overall the plan seems acceptable. In addition, the Division asked New River what their total exposure data will be and they stated that they plan to have a total of 400-500 subjects.

Nonclinical

5. Pharmacokinetic studies have shown that measurable levels of the intact prodrug are present in both animals and humans. Bridging studies conducted in repeat dose toxicity studies of NRP104 and d-amphetamine in both dogs and rats have shown that the toxicity of NRP104 (at least 18 fold higher exposure than humans) does not differ substantially from that of d-amphetamine. The only other component of the prodrug is lysine which is a normal constituent of the human body. Assuming that the amount of lysine in the prodrug, when ultimately metabolized, will not raise endogenous levels above the normal range, does the Division agree that no additional studies are needed to assess the toxicity of the prodrug?

   FDA Response: No. Juvenile animal studies are needed in rodent and nonrodent. These studies need to include evaluation of general toxicity parameters (including full histopathology) as well as developmental parameters. You may submit draft protocols for review and comment. These studies will be needed prior to the NDA submission

   The FDA agreed to provide the sponsor with comments on the design of these studies in the meeting minutes. Therefore, the following comments are included:

   The juvenile studies should be designed to assess general toxicity and drug-related effects on stage(s) of development in animals relevant to the intended patient population. To support clinical trials in 6-12 year old children, rats should be dosed from approximately postnatal day (PND) 10 to PND 60. Effects on neurobehavioral development need to be assessed during treatment (acute effects) and after an appropriate washout period (depending on the $t_{1/2}$ of NRP-104) following cessation of treatment (potential long-term effects). To avoid the confounding effects of repeated neurobehavioral testing, separate groups of animals must be used at the two assessment times. To avoid unnecessary use of animals, the same group of animals may be used to evaluate neurobehavioral effects during treatment and effects on reproductive parameters (which are to be assessed following cessation of treatment). The neurobehavioral assessment should include tests of sensory function, motor function, and learning and memory. The neuropathological evaluation should include examination of all major brain regions and cellular elements,

with particular attention to alterations indicative of development insult.

Dogs should be dosed from approximately 6-8 weeks to approximately 8-9 months of age. (If another species is to be used, the period of treatment would need to cover all developmental stages relevant to the intended patient population.) In addition to the parameters routinely assessed in general toxicity studies, the study should include the following: (a) an assessment of cardiovascular parameters, (b) a detailed neurological examination at the end of the treatment period (prior to the last dose) and at the end of the recovery period. Neurological examinations should include evaluation of gait(head posture and coordination [including cranial nerve reflexes papillary light reflex, palpebral reflex, pain perception, and gag reflex]) and evaluation of the neck, forelimbs, and hind limbs (including placing, spinal reflexes, and flexor reflex), (c) a hormonal and sperm assessment, conducted at the end of the treatment and recovery periods.

6. Does the Division agree that the nonclinical program conducted to date and the additional planned studies meet the regulatory requirements to support the proposed clinical program, and ultimately registration of the product for treatment of ADHD in 6-12 year olds?

   FDA Response: No. In addition to the juvenile animal studies, the in vitro mouse lymphoma assay (with colony sizing) needs to be repeated since the results suggested methodological problems (wide variability in values) and the equivocal response; alternatively, you may conduct an in vitro chromosomal aberration assay in mammalian cells. The in vivo micronucleus assay may need to be repeated using higher doses (i.e., doses associated with frank toxicity). According to the sponsor, self mutilation was considered a dose-limiting effect; however, there was no listing of self mutilation in the clinical signs data in the study report. If the sponsor believes that dose-limiting toxicity was observed in males and females in the in vivo study, further documentation to that effect needs to be provided. If such documentation cannot be provided, then the study will need to be repeated.

Chemistry Manufacturing and Controls

7. Does the Division agree with the release and stability specifications for both the Drug Substance and the Drug Product?

   FDA Response: Your current approach calculates impurities utilizing an area percent approach. Impurities should be calculated on weight percentage basis. You are currently investigating the [redacted] *All test methods will need to have specification limits (as opposed to "for information only"). In addition, a*

8. Does the Division agree that the [redacted] can be removed as a specification for the release of the Drug Substance?

   FDA Response: No, considerably more experience and data with the drug are needed before this can be determined.

9. Does the Division agree with the Bracketing Plan proposed for the stability testing of the Drug Product?

   FDA Response: The plan seems acceptable (see Question 7).

Additional Discussions:
New River Pharmaceuticals was reminded to submit all changes to any protocol to the IND.

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Regulatory Project Manager

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/s/

Russell Katz
9/21/04 09:54:52 AM