

APPLICATION NUMBER:
22-395

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**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*

NDA NUMBER

22-395

NAME OF APPLICANT / NDA HOLDER

NeurogesX, 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)

Qutenza

ACTIVE INGREDIENT(S)

Capsaicin [(E)-8-Methyl-N-vanillyl-6-nonenamide]

STRENGTH(S)

8% capsaicin (640 mcg/cm²)

DOSAGE FORM

Dermal Patch

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

6,239,180

b. Issue Date of Patent

May 19, 2001

c. Expiration Date of Patent

May 29, 2018

d. Name of Patent Owner

The Regents of the University of California

Address (of Patent Owner)

1111 Franklin Street

City/State

Oakland / California

ZIP Code

94067-5200

FAX Number (if available)

Telephone Number

(510) 987-9220

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

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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) (as listed in the patent) Does (Do) the patent claim(s) 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



Oct. 3, 2008

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
NeurogesX, Inc.

Address
2215 Bridgepointe Parkway, Suite 200

City/State
San Mateo, CA

ZIP Code
94404

Telephone Number
(650) 358-3300

FAX Number (*if available*)
(650) 649-1798

E-Mail Address (*if available*)

The public reporting burden for this collection of information has been estimated to average 20 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

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**PATENT INFORMATION SUBMITTED WITH THE
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a. United States Patent Number

6,248,788

b. Issue Date of Patent

June 19, 2001

c. Expiration Date of Patent

November 6, 2016

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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

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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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).	<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.2	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2	Patent Claim Number(s) (as listed in the patent) 1,5,6,7, 8, 9, 14	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
		<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> 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.) Qutenza is indicated for the prolonged reduction of neuropathic pain associated with postherpetic neuralgia.	

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.*

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Date Signed



Oct. 3, 2008

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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
NeurogesX, Inc.

Address
2215 Bridgepointe Parkway, Suite 200

City/State
San Mateo, CA

ZIP Code
94404

Telephone Number
(650) 358-3300

FAX Number (if available)
(650) 649-1798

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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.

EXCLUSIVITY SUMMARY

NDA # 22-395

SUPPL #

HFD # 170

Trade Name Qutenza

Generic Name Capsaicin 8% Patch

Applicant Name NeurogesX

Approval Date, If Known November 16, 2009

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)(2)

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?

7 years, orphan drug designation

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 drugproduct(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

Investigation #1 !

YES

Explain: !

!

! O

Explain:

N

Investigation #2 !

YES

Explain: !

!

! O

Explain:

N

(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: Robert Shibuya, M.D.

Title: Clinical Team Leader, DAARP

Date: November 16, 2009

Name of Office/Division Director signing form: Bob Rappaport, M.D.

Title: Director, Division of Anesthesia, Analgesia, and Rheumatology Products

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22395	ORIG-1	NEUROGESX INC	Qutenza

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

/s/

TANYA D CLAYTON
11/16/2009

BOB A RAPPAPORT
11/16/2009

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-395 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DAARP PDUFA Goal Date: 08/16/09 Stamp Date: 10/16/2008
clock extended 11/16/09

Proprietary Name: Qutenza

Established/Generic Name: capsaicin Patch 8%

Dosage Form: Patch

Applicant/Sponsor: Neurogesx

*Need to
DFS*

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: prolonged reduction of neuropathic pain associated with PHN

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

Reference ID: 2915871

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Action C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

needs to be
DFSeel

Pediatric Research and Equity Act Waivers

NDA #: 22-395

Supplement Type: N/A

Supplement Number:

Product name and active ingredient/dosage form: Qutenza (capsaicin Patch 8%)

Sponsor: Neurogesx

Indications(s): Prolonged reduction of Neuropathic Pain associated with Postherpetic Neuralgia (PHN)

(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

1. Pediatric age group(s) to be waived. Birth to age 16.
2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):
 - a. Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). If applicable, chose from adult-related conditions in Attachment I.

The reason for waiving pediatric assessment requirements is that the incidence of PHN in this age group is extremely low and Capsaicin 8% is therefore not likely to be used in a substantial number of patients.

[Redacted] (b) (4)

[Redacted] (b) (4) PHN is associated with older subjects (94% of cases are > 60 years). The likelihood of developing PHN after shingles increases with age; the risk of PHN is low (2%) in patients younger than 50 years of age, ~20% in those older than 50 years and approximately 35% in those over the age of 80 years [Opstelten et al. 2001].

Though reports of Herpes Zoster can be found in children [Watson 2001], none have been associated with postherpetic neuralgia [Rogers and Tindall 1972, Hope-Simpson RE 1975, Guess et al. 1985, Petursson G et al. 1998, Lee et al. 2006].

Additionally, NeurogesX has requested Orphan Drug designation for NGX-4010 for the management of neuropathic pain in patients with PHN and is awaiting FDA's decision on this matter. The Orphan Drug Request further supports an FDA decision to grant NeurogesX a waiver for pediatric studies for NGX-4010. The Agencies decision regarding Orphan Drug designation is not available.

REFERENCES

- 1) Pamela P. W. Lee, MBBS, et al , Herpes Zoster in Juvenile-Onset Systemic Lupus Erythematosus, Incidence, Clinical Characteristics and Risk Factors, *Pediatr Infect Dis J* 2006;25: 728–732
- 2) Gunnar Petursson, MD, et al: Herpes zoster in children and adolescents, *Pediatric Infectious Dis J*, 1998, p 905-908
- 3) R.E Hope-Simpson: Post Herpetic Neuralgia, Herpes zoster in General Practice
- 4) Roy S. Rogers III, MD et al: Herpes Zoster in Children and Adolescence, *Arch of Dermatology*, Volume 106, August 1972
- 5) H.A. Guess, MD, et al: Epidemiology of Herpes Zoster in Children and Adolescents: A Population-Based Study, *Pediatrics* Vol 76 No. 4 October 1985
- 6) Opstelten et al; Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database, *Family Practice*, (Oxford University Press)

Attachment I

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver

These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration
Alzheimer's disease
Amyotrophic lateral sclerosis
Atherosclerotic cardiovascular disease
Benign prostatic hypertrophy
Chronic Obstructive Pulmonary Disease
Erectile Dysfunction
Infertility
Menopausal and perimenopausal disorders
Organic amnesic syndrome
(not caused by alcohol or other psychoactive substances)
Osteoarthritis
Parkinson's disease
Postmenopausal Osteoporosis
Vascular dementia/ Vascular cognitive disorder/impairment

Cancer :
Basal cell
Bladder
Breast
Cervical
Colorectal
Endometrial
Gastric
Hairy cell leukemia
Lung (small & non-small cell)
Multiple myeloma
Oropharynx (squamous cell)
Ovarian (non-germ cell)
Pancreatic
Prostate
Renal cell
Uterine

1.3.3 DEBARMENT CERTIFICATION

NeurogesX, Inc. 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.



Susan Rinne, M.S.
Vice President, Regulatory Affairs

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-395 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Qutenza Established/Proper Name: capsaicin Dosage Form: patch 8%		Applicant: NeurogesX, Inc. Agent for Applicant (if applicable):
RPM: Tanya Clayton		Division: Anesthesia, Analgesia and Rheumatology Products
<p><u>NDA's:</u> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>N/A published literature</p> <p>Provide a brief explanation of how this product is different from the listed drug. The sponsor is referencing published literature for pharm/tox safety. This will be the first approved capaicin product. There are currently unapproved products on the market.</p> <p><input checked="" type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: July 8, 2009; October 23, 2009</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		August 16, 2009; November 16, 2009
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		<input checked="" type="checkbox"/> None

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

❖ Advertising (*approvals only*)
Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed (*indicate dates of reviews*)

- Requested in AP letter
- Received and reviewed

❖ Application ² Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments:	
❖ Application Integrity Policy (AIP) http://www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input type="checkbox"/> No
• If yes, exception for review granted (<i>file Center Director's memo in Administrative/Regulatory Documents section, with Administrative Reviews</i>)	<input type="checkbox"/> Yes
• If yes, OC clearance for approval (<i>file communication in Administrative/Regulatory Documents section with Administrative Reviews</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: <input type="checkbox"/>	April 8, 2009
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

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

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³ In	cluded
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/nonconsent by officers/employees	<input type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) November 16, 2009
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	November 16, 2009
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	N/A
❖ Original applicant-proposed labeling	N/A
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None
❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 5/29/08

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
❖ Original applicant-proposed labeling	
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	November 12, 2009
❖ Most recent applicant-proposed labeling	November 12, 2009
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM meetings: July 1, 7, 13, 20 and 28, 2009 <input checked="" type="checkbox"/> DMEDP May 5, 2009 <input checked="" type="checkbox"/> DRISK July 22, 2009 <input checked="" type="checkbox"/> DDMAC July 15, 2009 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	December 1, 2008 (signed off) November 16, 2009
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If approval action, OC clearance for approval 	<input checked="" type="checkbox"/> Not on AIP
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies <ul style="list-style-type: none"> Outgoing communications (<i>if located elsewhere in package, state where located</i>) Incoming submissions/communications 	<input checked="" type="checkbox"/> None
❖ Postmarketing Commitment (PMC) Studies <ul style="list-style-type: none"> Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment 	<input checked="" type="checkbox"/> None
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	Ack Letter (October 27, 2008); Filing Letter (December 24, 2008); Orphan Designation Letter (May 22, 2009); Discipline Review letter (June 4, 2009); Clock extension letter (August 5, 2009) AP Letter 11/16/09
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	

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

• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)	<input checked="" type="checkbox"/> Not applicable
• Regulatory Briefing (<i>indicate date</i>)	<input checked="" type="checkbox"/> No mtg
• Pre-NDA/BLA meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg April 3, 2008
• EOP2 meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg April 18, 2006 (CMC); January 24, 2006
• Other (e.g., EOP2a, CMC pilot programs)	N/A
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None November 13, 2009
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None November 13, 2009
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None July 10, 2009
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	July 10, 2009
• Clinical review(s) (<i>indicate date for each review</i>)	July 1, 2009; October 15, 2009
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	Clinical Review, page 144 (submitted February 4, 2009)
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Clinical Review July 1, 2009
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None Derm/Dental July 15, 2009
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ REMS	<input checked="" type="checkbox"/> None
• REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• Review(s) and recommendations (including those by OSE and CSS) (<i>indicate location/date if incorporated into another review</i>)	
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	May 29, 2009; June 18, 2009
• Bioequivalence Studies	N/A
• Clinical Pharmacology Studies	N/A
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	

⁵ Filing reviews should be filed with the discipline reviews.
Version: 5/29/08

❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None July 1, 2009
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None July 7, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None July 17, 2009
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None July 17, 2009
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None July 17, 2009; Oct. 27, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc Nov 13,2009
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None April 20, 2009 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None Nov. 6. 2009
• Branch Chief/TeamLeader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None May 14, 2009; July 1, 2009; September 15, 2009
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	CMC Review #1, page 121, May 14, 2009
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	

<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) 	<p>Date completed:</p> <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ➤ TBP-EER ➤ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>) 	<p>Date completed:</p> <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <p>Date completed:</p> <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
<ul style="list-style-type: none"> ❖ NDAs: Methods Validation 	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed

Appendix A to Action Package Checklist

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

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

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

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

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

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

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

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

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22395	----- ORIG-1	----- NEUROGESX INC	----- Qutenza

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

/s/

TANYA D CLAYTON
11/16/2009

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-395 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Qutenza
Established Name: capsaicin Patch
Strengths: 8%

Applicant: NeurogesX, Inc.
Agent for Applicant (if applicable):

Date of Application: October 13, 2008
Date of Receipt: October 16, 2008; major amendment July 30, 2009
Date clock started after UN:
Date of Filing Meeting: December 1, 2008
Filing Date: December 15, 2008
Action Goal Date (optional):

User Fee Goal Date: August 16, 2009;
November 16, 2009

Indication(s) requested: prolonged reduction of neuropathic pain associated with postherpetic neuralgia.

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

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 7
Other (orphan, OTC, etc.) Orphan

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

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

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

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

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

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

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

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

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

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

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

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

Additional comments:

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

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? Yes Years 7 years Orphan NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

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

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

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 63,354

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

- End-of-Phase 2 Meeting(s)? Date(s) April, 18, 2006 CMC/January 24, 2006 NO
Clinical

If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) April 3, 2008 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

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

Clinical

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

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 1, 2008

NDA #: 22-395

DRUG NAMES: Qutenza (capsaicin) patch for topical use

APPLICANT: NeurogesX, Inc.

BACKGROUND: This NDA was submitted as a 505(b)(2) application. The sponsor referenced published literature for clinical and non-clinical safety. The sponsor received Orphan drug designation on May 22, 2009.

ATTENDEES: Bob Rappaport, Sharon Hertz, Robert Shibuya, Neville Gibbs, Adam Wasserman, Lawrence Leshin, Dionne Price, Katherine Meaker, Suresh Doddapaneni, David Lee, Danae Christodoulou, Theodore Carver, Tanya Clayton

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

<u>Discipline/Organization</u>	<u>Re</u>	<u>viewer</u>
Medical:		Neville Gibbs
Secondary Medical:		
Statistical:		Kate Meaker
Pharmacology:		Lawrence Leshin
Statistical Pharmacology:		
Chemistry:		Ted Carver
Environmental Assessment (if needed):		
Biopharmaceutical:		David Lee
Microbiology, sterility:		
Microbiology, clinical (for antimicrobial products only):		
DSI:		Sherbet Samuels
OPS:		
Regulatory Project Management:		Tanya Clayton
Other Consults:		DDMAC- Michelle Safarik OSE-Mary Dempsey, Cheryl Wisemen Clinical Pharmacology

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

CLINICAL FILE REFUSE TO FILE

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

- 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 YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

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

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO

- Sterile product? YES NO

- If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:

Any comments: To be conveyed in 74 Day Letter:

Pharm/tox : Requested a point mutation assay with the isolated impurity tested up to the limit dose for the assay.

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

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

ACTION ITEMS:

- 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.
- If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
- If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Tanya D. Clayton
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

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

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (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.)

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

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

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

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

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If “No,” skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an “old” antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If “Yes,” skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES NO

If “Yes “contact your ODE’s Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If “No,” to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES NO

If “Yes,” (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If “No,” to (c) list the pharmaceutical equivalent and contact your ODE’s Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If “Yes,” to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12. NO

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

This application provides for a change in dosage form, from tablet to capsule.

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO
10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES NO
12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO
13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- Not applicable (e.g., solely based on published literature. See question # 7)
 - 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):
- NOTE:** *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
 - Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
 - 21 CFR 314.50(i)(1)(ii): No relevant patents.
 - 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Pharm/tox safety was based on published literature

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22395	ORIG-1	NEUROGESX INC	Qutenza

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

/s/

TANYA D CLAYTON
11/16/2009



NDA 022395

PDUFA GOAL DATE EXTENSION

Neurogesx, Inc.
2215 Bridgepointe Parkway
Suite 200
San Mateo, CA 94404

Attention: Susan Rinne, M.S.
Vice President, Regulatory Affairs

Dear Ms. Rinne:

Please refer to your October 13, 2008 new drug application (NDA), received October 16, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qutenza™ (capsaicin) 8% patch.

On July 31, 2009, we received your July 30, 2009, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 16, 2009.

If you have any questions, call Tanya Clayton, Regulatory Project Manager, at (301) 796-0871.

Sincerely yours,

{See appended electronic signature page}

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

SARA E STRADLEY
08/05/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring MD 20993

Tel 301-769-2110
Fax 301-796-9895

M E M O R A N D U M

Date: June 19, 2009

From: Joanna Ku, MD, Medical Officer, Division of Dermatology and Dental Products (DDDP)

Through: Jill Lindstrom, MD, Dermatology Team Leader, DDDP
Susan Walker, MD, Division Director, DDDP

To: Neville Gibbs, MD, Medical Officer, Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Robert Shibuya, MD, Medical Team Leader, DARRP
Sharon Hertz, MD, Deputy Division Director, DAARP
Bob Rappaport, MD, Division Director, DAARP

CC: Sue Kang, RPM, DDDP
Tanya Clayton, RPM, DAARP
Margo Owens, CPMS, DDDP
Julie Beitz, MD, Director, ODE 3, CDER
Maria Walsh, ADRA, ODE 3, CDER

Re: DDDP Consult 1150 (dated April 28, 2009):

- 1) Do you agree with the Applicant that all or some of the special dermal safety studies can be waived for this product that involves a single application of product by a physician or health care practitioner (HPC) for 60 minutes, with possible reapplication at 3 monthly or more intervals?
- 2) The Applicant used an unapproved marketed product to increase the tolerability of the patch application. The Applicant did not assess whether the anesthetic was essential although DAARP believes that the application of the active patch would not have been tolerated by most patients without some form of pre-treatment. The

Applicant did not use an approved topical anesthetic in any study in the clinical development program.

- a. A potential resolution to this issue would be to direct practitioners to use a “topical anesthetic” as pre-treatment without specifying which product to use. Does DDDP believe that these directions would pose any issues of safety or efficacy?
 - b. If DDDP believes that directing practitioners to use an unspecified topical anesthetic is unacceptable, please advise regarding how this product could be labeled.
- 3) Is the 1999 Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products still current or is it considered obsolete at this time?

Materials Reviewed:

- 1) NDA 22-395, Original Submission 000 dated October 13, 2008 (PDUFA due date August 16, 2009)
- 2) Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products (1999)
- 3) Guidance for Industry: Photosafety Testing (2003)

Review:

Regulatory Background:

NeurogesX Inc. (the Applicant) submitted an original NDA on October 13, 2008 for Qutenza™ (NGX-4010), which is capsaicin patch 8% for topical use. The proposed indication is “for the prolonged reduction of neuropathic pain associated with postherpetic neuralgia.” This high concentration 8% capsaicin product is a new molecular entity (NME). A variety of capsaicin creams, lotions, and patches containing much lower doses, generally in the ranges of 0.025% to 0.1% by weight, are sold without prescription for the treatment of neuropathic and musculoskeletal pain in the US. If approved, Qutenza will be available by prescription only.

On February 3, 2009, the Applicant and the Review Division (DAARP) held a teleconference to discuss the requirements for dermatology provocative studies. The following information is summarized from the Applicant’s minutes of the conference (as submission Sequence #0004 to the NDA). In these minutes, DARRP stated that issues regarding special dermal safety studies had not been discussed prior to filing. Had these issues been discussed, the absence of these studies would have constituted a filing issue. DARRP stated that given that capsaicin is a monographed drug (although not at this high

concentration) and the fact that there are no novel excipients in the product formulation, the Applicant should conduct these studies as soon as possible, but they are not required to be completed prior to the NDA action date. If for whatever reason these studies could not be completed during the NDA review period, their completion would be a post-marketing commitment (PMC). The Applicant agreed to either initiate these studies and to submit the results as a PMC, or to provide rationale on why these studies were not necessary. A follow-up email (dated February 4, 2009) sent by the Division to the Applicant listed the Agency's request for the following provocative studies.

1. Cumulative irritancy study(ies) to include at least 30 evaluable subjects. If sufficient irritation is noted for the product, in Phase 2/3 studies, and labeling contains sufficient warning regarding irritation, then the cumulative irritancy study may be waived.
2. Allergic (contact allergy/sensitization) studies to include at least 200 evaluable subjects.
3. Phototoxicity and photoallergenicity (photo contact allergy) studies which may be waived if there is no drug absorbance in the 280-700 nm spectrum. These studies may also be waived if the patch under study is opaque or the only indications for use are in areas where there is a minimal chance of exposure to UV light.

The Applicant reviewed these requests, and submitted rationale for requesting a waiver of these studies (Sequence #0015), which is the content of this Consult Review.

Clinical background:

Capsaicin is a selective agonist for the transient receptor potential vanilloid 1 receptor (TRPV1). The Applicant demonstrated that application of capsaicin causes the loss of epidermal innervation in humans, and this loss of peripheral nerve terminals is thought to be the mechanism of pain relief for this treatment.¹ The effectiveness of single application of Qutenza was studied primarily in two adequate and controlled Phase 3 clinical trials (Studies C116 and C117) in a total of 818 adult patients with moderate to severe post herpetic neuralgia (PHN). Patients were more than 6 months post vesicular crusting, and application was over intact skin. All patients had received pre-treatment prior to Qutenza with an unapproved topic anesthetic. Dr. Neville Gibbs, the DAARP clinical reviewer, independently verified that Qutenza was superior to a low-dose capsaicin control in treating the pain of PHN.

The capsaicin in Qutenza is a synthetic equivalent of the naturally occurring, pungent compound found in chili peppers. Though its long-term effect is anesthesia, the *initial* effect of topical capsaicin application is noxious, and appears to be due to the activation of TRPV1-expressing cutaneous nociceptors, which result in localized burning sensations, hyperalgesia, allodynia, and erythema. Due to the intense burning and other noxious sensation, a topical anesthetic was applied prior to application of the capsaicin

¹ CDER CAC Committee Memo (April 14, 2009)

patch in patients in the clinical studies. A cleansing gel (b) (4) was applied following patch removal to remove residual capsaicin from the treatment site. The local anesthetic used in the clinical studies was an unapproved over-the-counter product, L.M.X. 4%® lidocaine topical formulation and it was applied for 60 minutes. Although the Applicant did not formally assess whether the pre-treatment medication was essential, the DARRP review team believes “the application of the active patch would not have been tolerated by most patients in the clinical trials without some form of pre-treatment.”

The Applicant currently proposes the following Dosage and Administration instructions in the product labeling. Only a HCP could administer Qutenza. Before patch application, the skin area is to be anesthetized by pre-treatment with “a topical anesthetic to reduce discomfort associated with the application of Qutenza.” After removal of the topical anesthetic, the skin is washed and dried, and the Qutenza patch is applied to the skin. To ensure Qutenza maintains contact with the treatment area, a dressing, such as rolled gauze, may be used. Use only nitrile (not latex) gloves when handling Qutenza and when cleaning treatment areas. Qutenza is not to be applied to broken skin, or near eyes or mucous membranes. Treat acute pain during and following the application procedure with local cooling (such as an ice pack) and/or appropriate analgesic medication. After removal of the patch, the skin is applied a Cleansing Gel (supplied with Qutenza) and left on for approximately 1 minute before wipe off, followed by washing and cleaning of the skin. The recommended dose is a single, 60 minute application of up to 4 patches at one time. Treatment with Qutenza may be repeated every 3 months or “as warranted by the return of pain.”

DDDP has been consulted to help address the requirements for dermal safety provocative studies, and the labeling language regarding the application of pre-treatment anesthetic.

Question 1:

Do you agree with the Applicant that all or some of the special dermal safety studies can be waived for this product that involves a single application of product by a physician or health care practitioner (HPC) for 60 minutes, with possible reapplication at 3 monthly or more intervals?

DDDP Response:

Should the applicant agree to labeling that conveyed the risks for local adverse reactions (irritation and sensitization), this approach may be acceptable.

Application site adverse events and dermal irritation were studied in 1696 patients treated with Qutenza in Phase 2 and 3 studies, including 429 patients with repeated treatments. The most common reported adverse events (AEs) were application site reactions, which included erythema (39%), pain (43%), pruritus (9%), and papules (5%). It is important to note that these incidence rates represent AEs occurred even after application with 4% lidocaine pre-treatment. In addition, in the two Phase 3 pivotal studies, patients were permitted to use rescue opioid medications during and after treatment for relief of treatment-related discomfort. A rapid-onset, opioid-based oral pain medication, such as oxycodone hydrochloride oral solution (1 mg/mL; e.g., Roxicodone®) was administered

as needed while the patient was in the clinic. Additional opioid-based oral pain medication, such as hydrocodone bitartrate/acetaminophen, 5/500 as needed (PRN), was permitted post-treatment through Day 5. In both studies, rescue opioid pain medication use was higher in subjects receiving Qutenza compared to the Control groups.

Patients were also systematically evaluated for dermal irritation using a 0- to 7-point dermal irritation score (Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products, 1999)². Dermal irritation was common after Qutenza patch application as compared with Control. Most patients (89%) had a score of 1 or 2 (score of 1= minimal erythema, barely perceptible, and score of 2 = definite erythema, readily visible, minimal edema or popular response). Thus, there is sufficient evidence that Qutenza causes dermal irritation.

Given that existing clinical data already demonstrate that Qutenza is a dermal irritant, the Applicant has proposed a waiver of the requirement of a cumulative irritancy study, and to use labeling to warn users about the irritation potential of the product, as well as to state the incidence of AEs associated with application site reactions. DDDP finds this approach acceptable, based on the following rationale. Cumulative irritancy study may be waived, as the purpose of conducting such test is to determine whether irritancy potential exist for a product. Where the product formulation has already been shown to be significantly irritating, and will be identified as such in proposed labeling, cumulative irritancy study could be waived. We recommend, however, that the product label clearly communicate the substantial pain/burning invoking potential of the product, without minimizing the severity/extent of such potential. For example, the Adverse Reactions section of labeling should clearly state that the incidence of pain reflects the incidence of pain *after* pre-treatment with topical lidocaine anesthetics, since without pre-treatment with anesthesia, incidence of pain would certainly have been higher.

The Applicant also proposed a waiver for the contact allergy/sensitization study. In the pre-clinical setting, a delayed contact hypersensitivity study in guinea pigs was conducted, in which Qutenza was found to be “a weak sensitizer,” based on a relatively low incidence and mild severity of challenge reactions to the Qutenza patch in the test group. In the clinical setting, application site adverse events and dermal irritation have been studied in 429 patients in Phase 2 and 3 studies treated more than once with Qutenza, applied at least 6-12 weeks apart. Application site reactions were present in about 67% of PHN patients, and dermal irritation (i.e., dermal assessment score > 0) were present in >95% of PHN patients. Although the Applicant concluded that there was no increase in the incidence and severity of dermal irritation or application site events (including application site urticaria, or urticaria), thus demonstrating that with repeated treatment there was no evidence of dermal sensitization, this Reviewer questions that conclusion. On page 9, Tables 5 in the document titled Request for Waiver (Sequence #0015 to the NDA) it is shown that a subset of patients had an increase in dermal irritation score compared to treatment cycle 1 during subsequent cycles of treatment. Specifically, it appears that for some patients, during subsequent treatment cycles 2, 3, and 4, both at time points of immediately after patch removal and 1-2 hours after patch

² See Appendix

removal, the patients experienced an increase in dermal score compared to treatment cycle 1. Additionally, in a subset of patients, there was an increase in maximum dermal score compared to treatment cycle 1 (see table below, copied electronically from the Applicant's submission). Thus it appears that at least for a subset of patients, sensitization might have occurred with repeated exposures.

Table 5: Summary of Dermal Assessment Scores On Treatment Day By Treatment Cycle (Repeat-Treatment Studies in PHN Patients)

	NGX-4010 Treatment Cycle		
	2	3	4
Number of Patients	229	129	44
Immediately After Patch Removal	229	128	44
N (%) of patients with an increase in dermal score compared to treatment cycle 1	34 (14.8)	14 (10.9)	8 (18.2)
N (%) of patients with no change in dermal score compared to treatment cycle 1	158 (69.0)	90 (70.3)	25 (56.8)
N (%) of patients with a decrease in dermal score compared to treatment cycle 1	37 (16.2)	24 (18.8)	11 (25.0)
1-2 Hours After Patch Removal	215	117	37
N (%) of patients with an increase in dermal score compared to treatment cycle 1	29 (13.5)	15 (12.8)	4 (10.8)
N (%) of patients with no change in dermal score compared to treatment cycle 1	139 (64.7)	76 (65.0)	26 (70.3)
N (%) of patients with a decrease in dermal score compared to treatment cycle 1	47 (21.9)	26 (22.2)	7 (18.9)
Maximum Score On Day 0[1]	229	129	44
N (%) of patients with an increase in maximum dermal score compared to treatment cycle 1	27 (11.8)	11 (8.5)	8 (18.2)
N (%) of patients with no change in maximum dermal score compared to treatment cycle 1	169 (73.8)	93 (72.1)	26 (59.1)
N (%) of patients with a decrease in maximum dermal score compared to treatment cycle 1	33 (14.4)	25 (19.4)	10 (22.7)

Source: [Source Table 4.4.3.4.2.](#)

Furthermore, it appears that a subset of patients, albeit only a small minority, was observed to have maximum dermal scores of 3 or greater during subsequent treatment cycles, which is another indication suggestive of that dermal sensitization reactions might have occurred (see table below, copied electronically from the Sponsor's submission).³

³ It should be noted however, the Table 4 does not contains details about whether it was the same patients who had a score ≥ 3 during subsequent cycles (i.e., 2, 3, or 4), as who had a score of ≥ 3 during the first cycle. Also, during the 1st treatment cycle, there were patients who had a score of ≥ 3 .

Table 4: Maximum Dermal Assessment Scores and Number (%) of Patients with a Maximum Increase \geq 2 Points on NGX-4010 Treatment Days by Each Treatment Received (Repeat-Treatment Studies in PHN Patients)

	Number of NGX-4010 Treatments			
	1 (N = 370)	2 (N = 229)	3 (N = 129)	4 (N = 44)
Maximum Score on Day 0, n (%)				
0 No evidence of irritation	9 (2.4)	8 (3.5)	8 (6.2)	3 (6.8)
1 Minimal erythema, barely perceptible	88 (23.8)	58 (25.3)	39 (30.2)	12 (27.3)
2 Definite erythema, readily visible, minimal edema or papular response	251 (67.8)	156 (68.1)	78 (60.5)	27 (61.4)
3 Erythema and papules	16 (4.3)	6 (2.6)	4 (3.1)	2 (4.5)
4 Definite edema	4 (1.1)	1 (0.4)	0	0
5 Erythema, edema, and papules	1 (0.3)	0	0	0
6 Vesicular eruption	1 (0.3)	0	0	0
7 Strong reaction spreading beyond test site	0	0	0	0
Maximum Increase \geq 2 Points, n (%)				
Yes	254 (68.6)	157 (68.6)	79 (61.7)	27 (61.4)
No	116 (31.4)	72 (31.4)	49 (38.3)	17 (38.6)

These clinical data, together with the pre-clinical data in the guinea pig, suggest that Qutenza may be an allergic sensitizer in a subset of patients. The evidence is not conclusive but suggestive. The Sponsor could include in the labeling a warning that Qutenza may be a sensitizing agent, in which case a formal sensitization study could be waived. However, if the Sponsor does not wish to include that in the labeling, a formal sensitization study should be pursued to rule out the risk of sensitization.

Finally, the Applicant requested waivers for the phototoxicity and photoallergenicity (photocontact allergy) studies for the following reasons. Capsaicin has minimal UVA/UVB/visible light absorption in the 290 to 700 nm spectrum. The Applicant submitted a scan of the UV spectrum of capsaicin which demonstrates only a small absorption peak at 281. Furthermore, it is pointed out that patients are unlikely to have significant exposure while exposed to the drug because Qutenza is a dermal patch that is applied by a HCP in an indoor setting as an office procedure, to the skin area of pain for only 1 hour and then removed. Although the drug patch backing is not opaque, the label instructs that to ensure Qutenza maintains contact with the treatment area, a dressing, such as rolled gauze, may be used (i.e., rolled gauze would provide opaque backing to block out light). After removal of the Qutenza patch, a cleansing gel is applied to remove any residual capsaicin, followed by washing with soap and water, and drying, so any residual Qutenza remaining on the skin would be unlikely. Treatment is administered only once every 12 weeks (or more frequently, if necessary), and given that PHN most commonly presents in the dermatomes on the trunk, and that treatment is administered for 1 hour, the potential for sun exposure will be limited. This Reviewer agrees that all of these factors contribute to minimal light exposure with Qutenza application.

One out of 1615 patients receiving a total of 2471 treatment had an AE consisting of a photosensitivity reaction. This was a 40-year old Caucasian male with HIV-associated neuropathy (HIV-AN) who was treated for 60 minutes on both feet and ankles. The patient displayed a mild photosensitivity reaction bilaterally on the feet 51 days after patch application. The reaction resolved on day 76 and was considered possible related to treatment. The patient was also taking sulfamethoxazole-trimethoprim for pneumocystis prophylaxis, a medication with known phototoxicity/photosensitivity effects. Thus it appears there was only one isolated incidence of possible photosensitivity reaction that may or may not have been related to Qutenza. It should also be noted that the Sponsor is seeking an indication in PHN not in HIV-AN.

Photosafety and phototoxicity studies were performed in rats and demonstrated no dermal responses indicative of phototoxicity due to Qutenza applications. The primary irritancy and phototoxic potential of Qutenza was investigated when topically administered to rats (for 1, 2, or 3 hours) before exposure to UV radiation, at a dose equivalent to approximately 0.5 minimal erythema dose (MED) delivered in an exposure period of approximately ½ hour. Rats were examined immediately, and 1, 2, 4, and 6 hours after patch removal. Erythema resolved in all rats 1 hour after patch removal. The phototoxicity portion of the study utilized Qutenza patch application times of 1, 2, and 3 hours, an application time for the placebo patch of 3 hours, and a 2 hour time interval between patch removal and irradiation. 8-MOP was included as a positive control. No dermal responses indicative of phototoxicity occurred in any of the groups of rats that received Qutenza, as compared with dermal responses indicative of phototoxic responses, including erythema and scab formation occurred in the group of rats treated with 8-MOP.

Assuming that the Applicant's claim with regards to Qutenza's absorption spectrum is accurate (which should be independently verified by DRRRP chemistry/product reviewer), DDDP concur that phototoxicity and photoallergenicity studies may be waived. In general, if no components of the drug product absorb light corresponding to wavelengths of 290 to 700 nm (UVA, UVB, and visible), then an Applicant may request this these tests to be waived. Also, in general, phototoxicity studies may be waived if the use of the topical product is to be in an area not normally exposed to light, or under an opaque dressing, both which of which appear to be the case with Qutenza administration. It may be reasonable to include instructions in the labeling for limiting sun/light exposure to the area after Qutenza application.

Question 2:

The Applicant used an unapproved marketed product to increase the tolerability of the patch application. The Applicant did not assess whether the anesthetic was essential although DAARP believes that the application of the active patch would not have been tolerated by most patients without some form of pre-treatment. The Applicant did not use an approved topical anesthetic in any study in the clinical development program.

- a. **A potential resolution to this issue would be to direct practitioners to use a "topical anesthetic" as pre-treatment without specifying**

which product to use. Does DDDP believe that these directions would pose any issues of safety or efficacy?

- b. **If DDDP believes that directing practitioners to use an unspecified topical anesthetic is unacceptable, please advise regarding how this product could be labeled.**

DDDP Response:

It is unclear how the Agency could label the product based on these directions. The only pre-treatment experience in the clinical trials has been with L.M.X., therefore it would be problematic to instruct health care providers to apply a non-specified “topical anesthetic” prior to Qutenza application. However, to instruct the use L.M.X. 4% lidocaine cream (an unapproved product) would also be problematic, because unapproved products are usually not mentioned in the product labeling.

To resolve this issue, the Applicant has submitted a protocol for an open-label study (Study C123) of the tolerability of the use of topical EMLA™ (2.5% lidocaine/2.5% prilocaine cream), as pre-treatment for Qutenza in subjects with PHN. In this study (herein identified as “the Tolerability Study”), 20 patients with PHN in 8 centers would be pre-treated with EMLA cream for 60 minutes followed by a single 60-minute application of Qutenza. Painful areas of up to a maximum of 1000 cm² of skin will be pre-treated with EMLA cream. Subjects will be evaluated at the Screening Visit, Day 0 (the day of application), and Day 7, for a total of 3 visits to assess pain scores, dermal assessments, and AEs. To justify the use of EMLA instead of LMX, and to “bridge” the two products, the Applicant provided references of 4 studies^{4, 5, 6, 7} that demonstrate similar efficacy in anesthesia between 4% Lidocaine, and EMLA, prior to minor procedures.

We do not have sufficient details of L.M.X. and EMLA applications, e.g., whether L.M.X was applied with occlusion in the completed Phase 2/3 trials, and whether EMLA would be similarly applied with occlusion in the Tolerability Study. Occlusion of the skin can disrupt the cutaneous barrier, rendering the skin more permeable to penetration of an applied product. The magnitude of the disruption can be influenced by the vehicle of the pretreatment anesthetic, as well as by the occlusive regimen. Another issue would be the dosage of EMLA that would be applied. We note from the EMLA product labeling, there

⁴ Carter, El, Coppola CA, Barsanti FA. A randomized, double-blind comparison of two topical anesthetic formulations prior to electrodesiccation of dermatosis papulosa nigra. *Dermatol Surg* 2006 Jan; 32(1):1-6

⁵ Eichenfield LF, Funk A, Fallon-Friedlander S et al. A clinical study to evaluate the efficacy of ELA-Max (4% liposomal lidocaine) as compared with eutectic mixture of local anesthetics cream for pain reduction of venipuncture in children. *Pediatrics*. 2002 Jun; 109(6): 1093-9.

⁶ Friedman PM, Fogelman JP, Nouri K et al. Comparative study of the efficacy of four topical anesthetics. *Dermatol Surg* 1999 December; 25 (12):950-4.

⁷ Guardiano RA, Norwood CW. Direct comparison of EMLA versus lidocaine for pain control in Nd:YAG 1,064 nm laser hair removal. *Dermatol Surg*. 2006 Apr; 31 (12): 1747.

are different dosage and administration instruction for minor vs. major dermal procedures. For minor procedures such as intravenous cannulation and venipuncture, patients apply 2.5 g of EMLA over 20-25 cm² of skin surface for at least 1 hour. For major dermal procedures involving a larger skin area such as split thickness skin graft harvesting, patients apply 2 grams of EMLA Cream per 10 cm² of skin and allow EMLA to remain in contact with the skin for at least 2 hours. The dosing regimen, both by the vehicle and the dressing, could render the skin more susceptible to irritation and sensitization (which could impact safety), and could increase permeability of the product (which could impact efficacy and safety). It is not clear that the results with topical EMLA could be generalized to use of the product with other approved topical anesthetics.

Based on the results of this small and limited study, we may not know the true impact of the change in the proposed pretreatment regimen (from L.M.X. to EMLA) on the safety and efficacy of Qutenza; this information would typically be obtained in Phase 3 pivotal trials. We understand that at this time, DAARP has agreed with the proposed study protocol, and has informed the Sponsor that they may proceed with conducting the study. It appears that the Sponsor intends to proceed with the study as soon as possible so to obtain results and information before the approval, to allow labeling for the use of EMLA as pre-treatment. If DAARP does not require additional bridging data prior to NDA approval, at a minimum a longer term and more extensive study should be required as postmarketing activity to confirm that the use of EMLA as pre-treatment does not change the safety and efficacy profile of the capsaicin patch as it was studied using L.M.X. as the pretreatment. However, it should be noted that the answer that we are providing here is not intended to address whether or not the NDA has provided adequate information to support approval of patch for use with topical anesthetics other than that used in the pivotal trials.

Question 3:

Is the 1999 Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products still current or is it considered obsolete at this time?

DAAP Response:

The 1999 Guidance was published by the Office of Generic Drugs (OGD), not the Office of New Drugs (OND). The OGD Guidance pertained to generic drugs, not new drugs. Furthermore, the Guidance has been withdrawn and is considered obsolete.

Thank you for this consult, and please let us know if we could provide additional assistance.

Appendix

Dermal Response

0 = no evidence of irritation

1 = minimal erythema, barely perceptible

2 = definite erythema, readily visible; minimal edema or minimal papular response

3 = erythema and papules

4 = definite edema

5 = erythema, edema and papules

6 = vesicular eruption

7 = strong reaction spreading beyond application site

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

/s/

Joanna Ku
7/14/2009 11:03:16 AM
MEDICAL OFFICER

Jill Lindstrom
7/15/2009 03:05:52 PM
MEDICAL OFFICER

Susan Walker
7/15/2009 04:29:49 PM
DIRECTOR

505(b)(2) ASSESSMENT

Application Information		
NDA # 22395	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Qutenza Established/Proper Name: capsaicin Dosage Form: patch Strengths: 8%		
Applicant: Neurogesx, Inc.		
Date of Receipt: October 16, 2008		
PDUFA Goal Date: August 16, 2009/November 16, 2009 (major amendment)		Action Goal Date (if different):
Proposed Indication(s): management of neuropathic pain associated with postherpetic neuralgia		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published literature	Pharmacology/Toxicology Safety

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Reliance was limited to published studies of capsaicin pharmacology. The (b)(2) reference is scientifically valid as this is the active ingredient in Qutenza.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

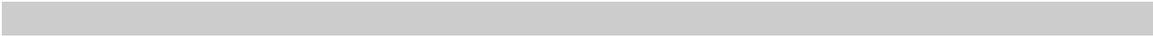
YES NO

If “NO,” proceed to question #5.

If “YES,” list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO



RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.
If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If “**NO**” to (a) proceed to question #11.
If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22395	ORIG-1	NEUROGESX INC	Qutenza

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/s/

TANYA D CLAYTON
11/16/2009



NDA 22-395

DISCIPLINE REVIEW LETTER

Neurogesx, Inc.
2215 Bridgepointe Parkway
Suite 200
San Mateo, CA 94404

Attention: Susan Rinne, M.S.
Vice President, Regulatory Affairs

Dear Ms. Rinne:

Please refer to your new drug application (NDA) dated October 13, 2008, received October 16, 2008 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qutenza™ (Capsaicin) 8% Patch.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Propose the minimum number of acceptable (b) (4) and criteria to be used in the final step of the capsaicin manufacturing process; this number is described as either (b) (4) in the application.
2. Provide additional information regarding (b) (4)
3. Provide additional information on quality control testing that you have performed on cut patches, to ensure that cut patches have acceptable properties, e.g. peel and adhesive forces. Include descriptions of the tests performed and the results of the tests. Provide a summary of clinical experiences in relation to the physical properties of the cut patches, including the range of sizes of cut patches used in clinical studies and any difficulties experienced in administering cut patches to patients.
4. You proposed to (b) (4)
(b) (4) This request should be submitted as a postmarketing prior approval supplement, after additional data on at least 10 commercial batches has been collected.

5. [REDACTED] (b) (4)
6. Increase the lower limit of the drug product specification for [REDACTED] (b) (4) content to [REDACTED] (b) (4) during the shelf life of the product, or provide justification for not doing so.
7. [REDACTED] (b) (4)
8. Provide supporting stability data for [REDACTED] (b) (4)
9. [REDACTED] (b) (4)
10. Per 21CFR 201.10(g), revise the product labeling so that the established name is at least half as large as the proprietary name and use a color for the text such that the established name has a prominence commensurate with that of the proprietary name, for example dark black [REDACTED] (b) (4)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Tanya Clayton, Regulatory Health Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Ali Al-Hakim, Ph.D.
Chief, Branch II
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Ali Al-Hakim

6/4/2009 06:30:51 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

MAY 22 2009

NeurogesX, Inc.
2215 Bridgepointe Parkway, Suite 200
San Mateo, California 94404

Attention: Susan Rinne
Vice President, Regulatory Affairs

Re: Designation request # 08-2695

Dear Ms. Rinne:

Reference is made to your request for orphan-drug designation submitted October 1, 2008, of capsaicin patch 8% (trade name: Qutenza™) for "management of neuropathic pain in patients with postherpetic neuralgia (PHN)." Please also refer to our letters of October 6 and November 13, 2008, and to your submission dated March 20, 2009.

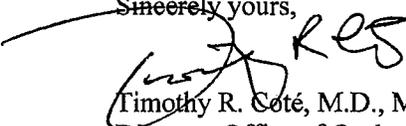
Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan-drug designation of capsaicin patch is granted for *management of neuropathic pain in patients with postherpetic neuralgia*. Please be advised that it is the active moiety of the drug and not the formulation of the drug that is designated.

Please note that if the above drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (see 21 C.F.R. 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the drug's designated use.

If you need further assistance in the clinical development of your drug, please feel free to contact Peter L. Vaccari, R.Ph., RAC, at (301) 827-3666. Please refer to this letter as official notification. Congratulations on obtaining your orphan-drug designation.

Sincerely yours,


Timothy R. Coté, M.D., M.P.H.

Director, Office of Orphan Products Development

NeurogesX, Inc.

2

cc:

HF-35/OP File # 08-2695

HF-35/Chron

HF-35/PVaccari

jb 5/19/09

DESIGNATION GRANTED

Executive CAC

Date of Meeting: April 14, 2009

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Al DeFelice, Ph.D., DCRP, Rotating Member
Adam Wasserman, DAARP, Team Leader
Steven Leshin, DAARP, Presenting Reviewer

Author of minutes: Steven Leshin

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

NDA 22-395

Drug Name: Capsaicin Patch 8% (Qutenza)

Sponsor: NeurogesX Inc.

Background:

Capsaicin is being developed as a topical patch to treat patients with peripheral neuropathic pain (post-herpetic neuralgia). Capsaicin is a selective agonist for the transient receptor potential vanilloid 1 receptor (TRPV1) which is a ligand-gated, non-selective cation channel preferentially expressed on small-diameter sensory neurons involved in the detection of painful or noxious sensations. In an exploratory IND, the Applicant demonstrated the loss of epidermal innervation in humans with a single 1-hour application of a 10% capsaicin containing solution, and this loss of peripheral nerve terminals is thought to be the mechanism of pain relief for this treatment. Due to the intense burning sensation associated with topical applications of capsaicin, a topical anesthetic is applied prior to application of the patch. Also a cleansing gel is applied following patch removal to remove residual capsaicin from the treatment site.

The carcinogenicity study was discussed and designed before it was determined that the Applicant's topical patch would be indicated for use as a one-time 60 minute application in a physician's office, with repeated application at 3 month intervals if necessary. The carcinogenicity study described here was also published in 2007.

Chanda S, Erexson G, Frost D, Babbar S, Burlew JA, Bley K.

26-Week dermal oncogenicity study evaluating pure trans-capsaicin in Tg.AC hemizygous mice (FBV/N). Int. J. Toxicol. 2007 Mar-Apr; 26(2):123-33

Tg.AC Mouse Study

The study design is indicated in the table below. Due to intense burning sensation when

applied to human skin in clinical studies a topical anesthetic is applied prior to application of the patch, and after patch application, residual capsaicin is wiped off with a specially formulated cleansing gel. These were necessary treatments in the mouse study as well, and therefore the study contained 7 treatment groups: vehicle control, 3 doses of capsaicin (applied as a solution; the high dose is similar to the human dose expressed as mg/cm² of application area), lidocaine topical anesthetic cream control, positive control, and untreated control groups.

Group 1		2	3	4 5		6	7
Group Type	Vehicle control	Capsaicin low	Capsaicin mid	Capsaicin high	Lidocaine control	Positive control	Untreated control
Anesthetic (30-45 min)	Lidocaine	Lidocaine	Lidocaine	Lidocaine	Lidocaine	No No	
Test Article (3 hours)	Vehicle (DGME)	Low	Mid	High	No T	PA (in DGME)	No
Application 1	X/week for 3 hrs	1X/week	2X/week for 3 hrs	-			
Cleansing Gel	Yes	Yes	Yes	Yes No		Yes	No
Dose (mg/mouse)	0	0.64	1.28	2.56 0		6.25 µg/application; 12.5 µg/week	0
Dose / application area (mg/cm ²)	0	0.16	0.32	0.64 0		1.56 µg/cm ² /twice weekly; 3.25 µg/cm ² /week	0

- Histopathological analysis (refer to the table below) of dermal masses obtained at necropsy from the site of capsaicin application revealed that, of the confirmed masses, most were benign squamous cell papillomas. The incidence of papillomas in the capsaicin groups was greater than in the vehicle control group, with a positive dose trend for papillomas in females. However, there was not a clear overall dose-response. The anesthetic control group and untreated control groups had a similar low incidence of papillomas as the vehicle control group. The positive control group was clearly positive, with most animals having squamous cell papillomas in the treatment area.
- As presented the study lacked the information that would allow standard Tg.AC analysis procedures employing weekly mass (papilloma) counts.
- The Applicant concluded that the study did not demonstrate capsaicin was carcinogenic in this animal model. "The frequency of dermal masses in the capsaicin-treated groups was not elevated in comparison to either the concurrent vehicle control (Group 1) or untreated control (Group 7)." "Topical application of capsaicin to male and female Model TGAC-T (hemizygous), FVB/NTac-Tg(v-Ha-ras)TG.ACled mice for 26 weeks resulted in no increased incidence of preneoplastic or neoplastic skin lesions." These statements are based on tables indicating dermal masses for the whole animal rather than the treatment area (the table was improperly labeled as indicating just treatment area), an excessively high number of masses in the untreated control group, and no statistical analysis.

In the table below, the top rows are the group identification numbers, treatments, number of animals initially treated, mortalities and survivors to the end of the study. The number of animals with at least one mass or papilloma at necropsy (combined unscheduled early death or euthanasia with scheduled at study termination) are presented for the Treated Skin or Non-Treated Skin. Non-Treated Skin means all skin other than the site of application (treatment site).

Summary of Results for Treated and Non-Treated Skin

Group 1			2		3		4 5				6		7	
Group Type	Vehicle control		Capsaicin low		Capsaicin mid		Capsaicin high		Lidocaine control		Positive control		Untreated control	
Gender M		F	M	F	M	F	M	F		F	M	F	M	F
N 25		25	25	25	25	25	25	25	25	25	25	25	25	25
Mortalities (unscheduled)	1	4	5	9	3	3	2	5	3	7	19	17	1	3
N at end of study	24	21	20	16	22	22	23	20	22	18	6	8	24	22

TREATED SKIN

Sponsor Summary [condensed by Reviewer from Chanda et al 2007: Tables 4, 5, 6, same as Module 2 Summary Tables].

Copyright Material

Reviewer Analysis from Individual Pathology Data Tables

Masses	0	0	2	2	7	3	4	3	0	1	21	20	0	1
Papillomas 0		0	1	1	4	2	1	2	0	0	21 ^a	17 ^a	0	1
Papillomas Combined Sexes	0		2		6		3	0			38 ^a	1		

* These incidences are the same as the statistical data set supplied by the Sponsor

NON-TREATED SKIN

Sponsor Summary [condensed by Reviewer from Chanda et al 2007: Tables 4, 5, 6, same as Module 2 Summary Tables].

Copyright Material

Reviewer Analysis from Individual Pathology Data Tables

Masses	7	11	7	6	21	6	11	17	11	10	24	20	16	10
Papillomas	3	2	1	2	6	3	3	8	4	4	10 ^b	10 ^b	6	5
Papillomas Combined Sexes	5		3		9		11	7			40 ^b	11		

Notes: Numbers represent animals with at least one mass or papilloma.

^a includes 2 animals with papillomas listed in the "treatment area", but were their sites were actually in other skin areas

^b there were 13 males and 8 females with masses that lacked adequate histopathology information; per protocol non-treated skin did not require histopathology

Study Comments:

Study Design and Appropriateness:

- Although the Tg.AC mouse model was determined as an adequate substitute for a 2-year (lifetime) bioassay at the time of the carcinogenicity study discussions (refer to Nov 9, 2004 EOP2 Meeting Minutes, discussion of question 7 and Oct 26, 2005 EOP2 Meeting Minutes, discussion of question 2) for this drug development program, previous studies in this model have generally not employed wiping of the skin with gauze multiple times each dosing day. This may be inappropriate in this model which has been shown to be sensitive to physical trauma. What impact this aspect of the treatment had on study outcome is not clear.
- A change in dosing strategy occurred half-way into the study that spread the dosing over a 2 day period. This mostly eliminated the unscheduled mortalities that occurred in most groups. While this change allowed more time for dosing and observation, and should not have impacted the study, there was too little explanation concerning this change. It was not mentioned why it took until half way through the study to alter the treatments to extend over a 2 day period. It is rare for deaths to occur in these 6 month studies, and more information should have been provided as to potential causes of these mortalities.

Statistical Analysis:

- The Applicant did not provide statistical analysis of the dermal masses or papillomas, and the basis for the Applicant's determination of lack of neoplastic potential of capsaicin was not presented. In general the methodology and presentation of results was unclear and misleading (tables did not reflect what they purported to indicate).
- Requests by the reviewing Statistician for a proper data set for this type of study, resulted in submission of only the presence or absence of masses, lacking the number of masses observed.

Results and Presentation:

- No pathology report was submitted, although summary and individual data tables were provided, but with insufficient explanation to allow for independent review of the data.
- The study report presentation was not an accurate reflection of the data in the individual animal study tables and the individual study tables, specifically Appendices 6 and 11 appeared to be incomplete and inconsistent with the stated methodology.

Executive CAC Recommendations and Conclusions:

- The Committee determined the study to be invalid, noting concerns with the conduct of the study, collection of data, summarization and presentation of data, data analysis and interpretation of the study.
- The Committee recommended that DSI should investigate this study.

- The Committee noted the published paper by Chanda et al., 2007 which reported this study as negative. The Committee did not conclude the study was negative and the study appears to have a positive trend for papillomas in females.

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

cc:\

- /Division File, DAARP
- /AWasserman, Team leader, DAARP
- /LSLeshin, Reviewer, DAARP
- /TClayton, CSO/PM, DAARP
- /ASeifried, OND IO

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/s/

David Jacobson-Kram
4/20/2009 01:56:08 PM

Clayton, Tanya

From: Greeley, George
Sent: Monday, April 13, 2009 10:28 AM
To: Clayton, Tanya
Cc: Mathis, Lisa; Stowe, Ginneh D.
Subject: NDA 22-395 Qutenza

Importance: High

Hi Tanya,

The Qutenza (capsaicin patch) full waiver was reviewed by the PeRC PREA Subcommittee on April 08, 2009. The Division recommended a full waiver because studies would be impossible or highly impracticable and because the disease/condition does not exist in children. The PeRC agreed with the Division to grant a full waiver for this product.

However, the PeRC has asked that the Division change the pediatric page to reflect the reason for waiver as too few children with disease/condition to study.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
1903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

 Please consider the environment before printing this e-mail.

From: [Clayton, Tanya](#)
To: ["Elda Tzoumaka";](#)
cc: [Clayton, Tanya;](#)
Subject: Information Request
Date: Thursday, January 29, 2009 4:20:51 PM
Attachments: [data-analysis-req.doc](#)

Hello Elda,

Please find attached an information request from our Statistical review team. Upon review, please let me know when you expect to provide a response.

Kind Regards,

*Tanya D. Clayton
Regulatory Health Project Manager
Food and Drug Administration
Division of Anesthesia, Analgesia, & Rheumatology Products
(301) 796-0871 Phone
Tanya.Clayton@fda.hhs.gov*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22395	ORIG-1	NEUROGESX INC	Qutenza

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/s/

TANYA D CLAYTON
11/18/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-395

Neurogesx, Inc.
2215 Bridgepointe Parkway
Suite 200
San Mateo, CA 94404

Attention: Susan Rinne, M.S.
Vice President, Regulatory Affairs

Dear Ms. Rinne:

Please refer to your new drug application (NDA) dated October 13, 2008, received October 16, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Qutenza™ (Capsaicin patch, 8%).

We also refer to your submission dated December 11, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is August 16, 2009.

During our filing review of your application, we identified the following potential review issue:

Based on review of the April 22, 2008, correspondence, the impurity, cis-capsaicin, in your product Capsaicin Patch 8% (w/w), is incompletely qualified at this time in that it is lacking genetic toxicology safety support for mutagenicity. A point mutation assay with the isolated impurity tested up to the limit dose for the assay is required. If a positive test result is obtained, a second alternative assay should be conducted such as the in vitro mouse lymphoma assay. Provide an estimated date for this study's submission.

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

- a. The impurities were not included in the certificates of analysis submitted with the original nonclinical studies. Include the report(s) for the analysis of cis-capsaicin in drug substance lots referenced in Table 2 and Table 4 of the April 22, 2008, submission.
- b. Provide a toxicological assessment of the cleansing gel and its components and justification for its safety.
- c. Submit the stability data in electronic format for the following attributes: [capsaicin assay, DGME content, adhesive force, water content, total impurities, cis-capsaicin, in vitro dissolution] of the capsaicin patch 8% and [viscosity and water content] of the cleansing gel respectively when stored at the room temperature condition. The column headings should include Attribute/Test, Batch Number, Package Type, Time in Months, and Test Result. The order of the columns is immaterial; however, TIME and TEST RESULT have to be numeric variables. Please submit the data files as SAS transport file(s). As an extrapolated shelf life is desired, please augment the data files with time points and missing test results beyond the desired shelf life.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients 0 to 16 years of age.

If you have any questions, call Tanya Clayton, Regulatory Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
12/24/2008 11:20:59 AM



NDA 22-395

NDA ACKNOWLEDGMENT

Neurogesx, Inc.
2215 Bridgepointe Parkway
Suite 200
San Mateo, CA 94404

Attention: Susan Rinne, M.S.
Vice President, Regulatory Affairs

Dear Ms. Rinne:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Capsaicin patch 8%

Date of Application: October 13, 2008

Date of Receipt: October 16, 2008

Our Reference Number: NDA 22-395

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 15, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable

clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Tanya D. Clayton
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Tanya Clayton
10/27/2008 03:02:06 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 63, 354

NeurogesX, Inc.
2215 Bridgepointe Parkway
Suite 200
San Mateo, CA 94404-5067

Attention: Patricia Taylor
Senior Director Regulatory Affairs

Dear Ms. Taylor:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (capsaicin) patch, 8%.

We also refer to the meeting between representatives of your firm and the FDA on March 6, 2008. The purpose of the meeting was to obtain Agency guidance regarding your upcoming New Drug Application submission.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Tanya Clayton
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 6, 2008

TIME: 2:00-3:00 pm

LOCATION: White Oak, Building 22, Conference Room 1315

APPLICATION: IND 63, 354

DRUG NAME: (b) (4) (Capsaicin Patch), 8%

INDICATION: Dermal Analgesic for Neuropathic Pain

TYPE OF MEETING: Type B, Pre-NDA

MEETING CHAIR: Sharon Hertz, M.D., Deputy Division Director

MEETING RECORDER: Tanya Clayton, Regulatory Project Manager

FDA Attendees	Title
Bob Rappaport, M.D.	Director
Sharon Hertz, M.D.	Deputy Division Director
Mary Purucker, M.D.	Clinical Team Leader
Neville Gibbs, M.D.	Clinical Reviewer
Lawrence Leshin, Ph.D.	Pharmacology/Toxicology Reviewer
Danae Christodoulou, Ph.D.	Pharmaceutical Assessment Lead
Dionne Price, Ph.D.	Statistics Team Leader
Joan Buenconsejo, Ph.D.	Statistics Reviewer
Tanya Clayton, B.S.	Regulatory Project Manager
NeurogesX, Inc. Attendees	Title
Keith Bley, PhD	Senior Vice President, Nonclinical Research & Development
Russell Kawahata, Ph.D.	Vice President, Pharmaceutical Science
Shiao-ping Lu, MS	Director, Biometrics
Susane Rinne, MS	Vice President, Regulatory Affairs
Patty Taylor, BS	Senior Director, Regulatory Affairs
Jeffrey Tobias, MD	Chief Medical Officer

Elda Tzoumaka, MS	Manager, Regulatory Affairs
Trudy Vanhove, MD, Ph.D.	Senior Director, Clinical Development
(b) (4)	Regulatory Consultant

BACKGROUND:

On October 30, 2007, the Sponsor requested a meeting to discuss their planned New Drug Application (NDA) submission that is currently planned for the second half 2008. The drug product is (b) (4) (capsaicin) patch, 8% and it is to be indicated as a dermal analgesic for neuropathic pain. The purpose of this meeting was to gain Agency guidance regarding any unresolved issues regarding filing their application. The Sponsor also wanted to provide the Agency with a brief overview of what will be contained within the upcoming application.

On March 5, 2008, the Sponsor was provided written responses to the questions posed within their February 6, 2008 background package. Consequently, the Sponsor requested to focus on questions 12, 13, 14 a/b, and 15a. The Sponsor also requested to have a future teleconference with CMC and Pharmacology/Toxicology once they have had time to further analyze the Agency's feedback.

The questions are presented below in *italicized* text. Agency responses are bolded. Discussion is presented in normal text.

Preliminary Discussion

Following introductions the Sponsor provided a brief presentation during which they demonstrated how the capsaicin patch is to be used. They also took questions from the Agency regarding its intended use. The Sponsor then agreed to proceed directly to the questions for discussion.

CLINICAL / STATISTICS

1. *NeurogesX has submitted an outline of the contents of the Integrated Summary of Efficacy (ISE) in Section 7.2 and a mock ISE report in Appendix B.*

Question 1a. Does the Agency agree with the proposed ISE presentation and analyses?

FDA Response:

We are in agreement with the organization and the presentation of your ISE data and proposed analyses.

Discussion

No further discussion was required.

Question 1b. In Section 7 of the ISE, the primary model proposed to investigate efficacy across studies contains two covariates, baseline pain score and gender in addition to the treatment effect. These two covariates have consistently demonstrated a significant contribution to the primary endpoint across studies. In some of the previous pivotal studies, other covariates such as pre-LMX pain score etc. were included in the primary endpoint analysis but these effects were not consistent, and therefore, they are not included in the proposed model. Additional analyses for other covariates to be added to the efficacy model will be performed using stepwise ANCOVA (ISE Section 8). Does the Agency agree with this approach?

FDA Response:

In general, we have no substantive disagreement with your approach to the presentation of efficacy data. The proposed presentation of summary tables of efficacy in Section 7 of the integrated summary of efficacy (ISE) is acceptable.

In Section 8 of the ISE, you proposed to analyze the data using the total efficacy population. The main purpose of the ISE is to explain how the results of the individual studies support the claims being made. Pooled analyses are not usually very helpful in this regard with the exception of required analyses by age, sex and race. Additional analyses may be performed; however, little weight will be given to the results from these analyses.

Discussion

No further discussion was required.

2. NeurogesX has submitted an outline of the contents of the Integrated Summary of Safety (ISS) in Section 7.3 and a mock ISS report in Appendix C.

Question 2a. Does the Division agree with the proposed ISS presentation and analyses?

FDA Response:

In general, we concur with your proposed presentation of the ISS and analyses. However we do not concur with how you handled the proposed AE's occurring as a result of "inadvertent capsaicin contamination". AE's occurring on a date of treatment that may be related to contamination of non-treated areas by capsaicin, must be counted as AE's. In addition, subjects who experience coughing when removing the patch must be listed as AE's and not handled separately.

Discussion

The Sponsor agreed to provide and separate the presentation of the AEs mentioned for ease of review.

Question 2b. Study C118 enrolled subjects that previously completed other NGX-4010 studies. Subjects in C118 received up to 4 treatments over the course of one year. For the ISS, subjects from C118 are summarized by number of treatments they received in C118, rather than the total number of treatments they received across all studies. This approach is proposed to accommodate the variable elapsed time between the end of the prior study and enrollment into C118 (the maximum time from the previous study is 29.6 months (~two and a half years)). Does the Agency agree with this approach?

FDA Response:

We consider your attempt to eliminate the variability in the lapse time between the end of the prior study and enrollment in Study C118 to be reasonable.

Discussion

No further discussion was required.

Question 2c. Healthy volunteers from studies C101 (N=20) and C115 (N=36) were treated at multiple sites on the thighs at a maximum area/site of 27.5 cm², and at doses ranging from 30 min to 120 min. Given that NGX-4010 exposure for these subjects was on normal and not neuropathic skin and that they could have been simultaneously exposed to multiple doses, adverse events for these subjects have been summarized separately in the ISS. Does the Agency agree with this approach?

FDA Response:

We concur that it is appropriate to analyze the data obtained from healthy volunteers studies separate from neuropathic skin and based on area of exposure, location of exposed area on the body and particularly time/duration of exposure to capsaicin, from the other AE's encountered and summarized in the ISS.

Discussion

No further discussion was required.

3. NeurogesX proposes to submit the CRTs utilizing Submission Data Tabulation Model (SDTM) version 3.1.1. The contents of the data package (CD included in Appendix D) include the following:

- Database structure and sample data for the proposed integrated efficacy data in ADaM format (version 2.0)
- Database structure and sample data for a pivotal phase 3 study in SDTM format (version 3.1.1). A sample of the Define.xml is also attached for metadata presentation.

Question 3a. Are the statistical reviewers in agreement with the content, structure and format of the efficacy ADaM dataset?

FDA Response:

The content, structure, and format appear reasonable.

Discussion

No further discussion was required.

Question 3b. Do the statistical reviewers have comments regarding other datasets (ADaM or SDTM) or the presentation of the metadata?

FDA Response:

We do not have any comments regarding other datasets or the presentation of the metadata.

Discussion

No further discussion was required.

Question 3c. Do the statistical reviewers wish to receive the programming code for statistical analyses performed?

FDA Response:

Yes, provide the programming code for the statistical analyses to facilitate the review.

Discussion

No further discussion was required.

Question 3d. With the provision of SDTM data sets, does the Division agree that submission of patient profiles is not necessary?

FDA Response:

With the provision of SDTM data sets, we agree that the submission of patient profiles is not necessary.

Discussion

No further discussion was required.

Question 4. *Does the Division have any update as to the acceptability of the proposed trade name, [REDACTED]™ (subject of IND 63,354 submission - Serial No. 139, 7 September 2007).*

FDA Response:

The acceptability of the proposed trade name of [REDACTED]™ is pending results of the consultation with DDMAC and DMETS/OSE.

Discussion

No further discussion was required.



Discussion

No further discussion was required.

Question 5b. *Safety data on over 1500 subjects exposed to NGX-4010 will be submitted in the NDA for PHN and HIV-AN. In addition to the subjects treated in the controlled PDN 12-week efficacy study, at least 100 subjects will continue to be followed for at least six months in the open-label long-term safety trial. Will these studies provide a safety database sufficient to support an approval of NGX-4010 for the treatment of subjects with PDN?*

FDA Response:

The proposed number of subjects exposed and the duration of exposure appears reasonable to address the question of product safety in the proposed population as long as no safety signals are identified that would require additional information to understand. However, the decision regarding the adequacy of the safety database to support approval will be a review issue.

Discussion

No further discussion was required.

Question 5c.

(b) (4)

FDA Response:

Response pending submission of a full protocol.

Discussion

No further discussion was required.

Question 5d. In past NGX-4010 trials, 173 subjects have been evaluated for plasma levels of capsaicin and capsaicin metabolites. Low, transient systemic levels of capsaicin were observed in only 30 of 96 of the PHN subjects (31%), 3 of 44 HIV-AN subjects (7%) and 1 of 33 PDN subjects evaluated (3%). Using a high sensitivity assay (LLOQ=0.5 ng/mL), capsaicin metabolites have never been detected in any subject. Among the HIV-AN and PDN subjects, both of which received treatment to the feet, the C_{max} detected was 1.75 ng/mL (HIV-AN) and 0.516 ng/mL (PDN). We believe these data sufficiently demonstrate that treatment of PDN subjects with NGX-4010 will not lead to significant systemic exposure in any PDN subjects. Further PK sampling in the two proposed PDN is therefore not indicated. Does the Agency agree?

FDA Response:

Yes. Your proposal is acceptable.

Discussion

No further discussion was required.

Question 5e.

(b) (4)

FDA Response:

(b) (4)

(b) (4)

Discussion

No further discussion was required.

CHEMISTRY, MANUFACTURING & CONTROLS

DRUG SUBSTANCE

The criteria by which

(b) (4)

are confirmed as Regulatory Starting Materials (RSM) for the capsaicin manufacturing process are presented (Section 9.2).

Question 6a. Does the agency concur that the proposed specifications are appropriate for (b) (4)?

FDA Response:

Yes. Include the specifications and supplier qualifying criteria for (b) (4) in the NDA.

Discussion

No further discussion was required.

Question 6b. Does the agency concur that the proposed specifications are appropriate for (b) (4)?

FDA Response:

Yes, specifications for (b) (4) are acceptable.

(b) (4)

In the Pharmaceutical Development

Report of the NDA, include supporting data from purging studies and batch analysis data, to justify the proposed specification for impurities, e.g., (b) (4)

Discussion

No further discussion was required.

NeurogesX has included the proposed final release specifications for the API. (Section 9.2).

Question 7. Does the Agency concur that these specifications are appropriate?

FDA Response:

Yes. In addition, provide justification for not including [REDACTED] (b) (4)
[REDACTED] **in the specifications of the drug substance.**

Discussion

No further discussion was required.

The commercial manufacturing process and process validation for Capsaicin Drug Substance are presented (Section 9.2).

Question 8. Does the Agency concur that this validation strategy is appropriate to validate the API process [REDACTED] (b) (4)?

FDA Response:

The validation approach is acceptable. [REDACTED] (b) (4)

Discussion

No further discussion was required.

DRUG PRODUCT

Capsaicin release (dissolution) from the patch is evaluated using a standard dissolution apparatus for modified release dosage forms with subsequent analysis by HPLC. Six patches are used for the testing for the in vitro release procedure. (Section 9.3).

Question 9. *NGX proposes that for testing of the capsaicin patch, the in vitro drug release testing with* [REDACTED] (b) (4)

[REDACTED] Does the agency concur with this approach?

FDA Response:

This approach is acceptable. [REDACTED] (b) (4)
[REDACTED]. **Include supporting dissolution data, e.g., from developmental and clinical batches, in the Pharmaceutical Development Report of the NDA, to demonstrate robustness and discriminatory ability of the dissolution method.**

Discussion

No further discussion was required.

(b) (4)
Determination of this parameter does not appear to be critical to ensure the patch functions as intended. (Section 9.3).

Question 10. Based on the data provided, does the Agency concur that determination of this parameter is not critical to ensure the patch functions as intended (b) (4)
is not a critical parameter?

FDA Response:

Based on the rationale presented in the briefing document, (b) (4)
does not appear to be a critical parameter to drug product quality and performance. Include in the PDR of the NDA the proposed justification and a summary of the supporting data, e.g., (b) (4)

Discussion

No further discussion was required.

NeurogesX has included the final analytical methods and proposed final release specifications for the capsaicin patch. (Section 9.3).

Question 11. Does the Agency concur that these methods and specifications meet the requirements of ICH Q6 A?

FDA Response:

Yes. The proposed drug product specifications are acceptable.

Discussion

No further discussion was required.

CLEANSING GEL

(b) (4)

Further discussion is in Section 9.4.

Question 12. Does the Agency concur with the use of (b) (4) based on the supporting information provided?

FDA Response:

Yes. Include the NF specifications for testing of (b) (4) in the NDA.

Discussion

The Sponsor informed the Agency that the vendor will not provide reference to the DMF for the (b) (4) Dr. Christodoulou stated that the Sponsor must specify in the NDA the supplier of (b) (4) include the specifications, supporting Certificate(s) of Analysis and a commitment that every batch will be tested according to the proposed specifications.

Question 13. Does the Agency concur that the specifications for the Cleansing Gel are appropriate and acceptable?

FDA Response:

The proposed specifications are acceptable. In addition, include microbial preservative effectiveness testing, and identity and assay of the major ingredient, (b) (4) or justify to the contrary.

Discussion

The Sponsor agreed to include microbial preservative effectiveness testing and to develop a new assay for (b) (4) Dr. Christodoulou indicated that the assay for the major component provides an additional identification test for the gel. The Sponsor stated that if they perform the assay of the major component, it seems redundant to also perform the functionality test for the gel. Dr. Christodoulou requested that the Sponsor include data to support their rationale in the Pharmaceutical Development Report (PDR) of the NDA. The Sponsor stated they will provide justification for removal of the functionality test in the NDA and provide a validated analytical assay for (b) (4)

The removal of residual capsaicin after patch removal from the skin is considered important for the safe use of the product. To complete treatment, following removal of the patch, cleansing gel is applied as a first step in removing residual capsaicin on the surface of the skin. The functionality testing of the cleansing gel and cleansing procedure performance are discussed in Section 9.4.

Question 14a. *Does the Agency concur with the method described to demonstrate the function of the cleansing gel?*

FDA Response:

The method described for removing the residual capsaicin appears to be adequate.

Discussion

Refer to discussion in Question 13.

Question 14b. *Does the Agency concur with the strategy described to demonstrate the cleansing procedures ability to remove of residual capsaicin?*

FDA Response:

The strategy described to demonstrate the cleansing procedures ability to remove residual capsaicin appears to be adequate.

Discussion

Refer to discussion in Question 13.

Cleansing Gel is manufactured as a (b) (4) tested and released, and subsequently filled into (b) (4) tubes. The Cleansing Gel has been filled into (b) (4) 50 gram (b) (4) tubes and stability up to 48 months performed. The proposed tube size for the commercial product is 50 grams. The stability data, ongoing stability plans and stability commitment proposal are summarized in Section 9.4.

Question 15a. *Does the Agency concur that the stability plan and proposal for establishing the shelf life for the Cleansing Gel are appropriate and acceptable?*

FDA Response:

The proposed stability plan is acceptable.

In addition, provide an evaluation of leachables/extractables of the container/closure system (tube) with the gel.

Discussion

The Sponsor inquired as to the purpose of evaluating the leachables/extractables since the container/closure system is used by many companies. Dr. Christodoulou responded that (b) (4) is considered a novel excipient and sufficient justification needs to be

provided to support that (b) (4) is equivalent to (b) (4). The sponsor agreed to provide evaluation of leachables/extractables, as per USP<661>.

Dr. Christodoulou inquired whether the Sponsor generated supporting data to ensure the physical integrity of the patch once it is cut, i.e., that the patch does not come apart when cut to size as proposed. The Sponsor stated they have data from their *in-vitro* dissolution studies to demonstrate no impact. Dr. Christodoulou advised them to include the data within the PDR of their NDA. In addition, she recommended they include a physical testing of the pieces, e.g., peel and adhesive strength tests. The Sponsor agreed to include the requested information within the NDA.

Question 15b. Does the Agency concur the stability data and plan will support the proposed shelf life of 36 months?

FDA Response:

Expiration dating of the gel will be assessed as per ICH Q1E, based on available real time data, and statistical analysis, as applicable.

ADDITIONAL CMC COMMENTS

Provide Drug Master File references and Letters of Authorization in the NDA, for the (b) (4) as applicable.

Provide a list of manufacturing facilities with full addresses and verification that they are ready for cGMP inspections. For any foreign facilities, provide a name contact with telephone number at the site.

REGULATORY/ADMINISTRATIVE

Question 16. (b) (4)

(b) (4)

FDA Response:

(b) (4)

Discussion

(b) (4)

ADDITIONAL COMMENTS:

PHARMACOLOGY/TOXICOLOGY

1. Any impurity or degradation product of the Drug Substance or Product that exceed ICH thresholds should be adequately qualified as per ICHQ3A and ICHQ3B(R2), respectively. Adequate qualification should include:
 - Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - Repeat dose toxicology of appropriate duration to support the proposed indication. For acute or highly intermittent use a 2-week study in a single species will be acceptable.
2. For the Cleansing Gel, present a toxicological assessment of its components and provide justification for its safety under the conditions of proposed use.
3. **Cross-Species Safety Margin Assessment**
For the nonclinical labeling sections, provide safety margin values based on concentration/unit area of patch dermal/local comparisons and based on toxicokinetic AUC comparisons for systemic comparisons.
4. **Topical Anesthetic Interaction**
Incorporate into the summary, commentary on the use of topical anesthetics (asa class and if necessary as individual products), its necessity and the potential safety issues that may arise from interaction with components of the capsaicin patch.

CLINICAL COMMENTS

1. Submit CRF's & narrative summaries for all Deaths, SAE's and "adverse dropouts" or drop-outs related to adverse events.
2. Submit the Coding Dictionary- used for mapping investigator verbatim terms to preferred terms
3. Submit AE datasets containing full MedDRA Hierachy, including primary, secondary and preferred terms.
4. Clarify whether topical lidocaine or LMX will be applied prior to capsaicin patch application as this will affect risk/benefit analysis
5. A pediatric development plan must be submitted with the NDA application

LABELING COMMENTS

Common PLR Labeling Deficiencies

Highlights:

- 1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]**
- 2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]**
- 3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product].
[See 21 CFR 201.57(a)(1)]**
- 4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]**
- 5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning."
Refer to
<http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).**
- 6. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].**
- 7. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:**

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

8. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
9. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].
10. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
11. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
12. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
13. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Contents (Table of Contents):

14. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
15. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
16. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
17. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
18. When a subsection is omitted, the numbering does not change. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

8.1 Pregnancy
8.3 Nursing Mothers (not 8.2)
8.4 Pediatric Use (not 8.3)

8.5 Geriatric Use (not 8.4)

19. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:
“*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI):

20. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
21. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
22. Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.
23. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not *See Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
24. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
25. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
26. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication

Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

- 27. There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.**
- 28. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.**
- 29. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.**
- 30. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.**
- 31. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.**
- 32. Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.**

Key Discussion Points/Action Items

The Sponsor agreed to provide the following information within their NDA:

- 1. AE’s that occurred on the day of treatment,**
- 2. ^{(b) (4)} supporting specifications, the Certificate of Analysis and a commitment that every batch will be tested,**
- 3. microbial preservative effectiveness testing and develop a new assay for ^{(b) (4)}**
- 4. evaluation of leachables/extractables pas per USP <661>,**
- 5. data on the physical integrity of the patch once it is cut.**

Linked Applications

Sponsor Name

Drug Name

IND 63354

NEUROGESX INC

CAPSAICIN DERMAL ANALGESIC
PATCH

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

/s/

SHARON M TURNER RINEHARDT

04/03/2008

signing for Tanya Clayton



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63,354

NeurogesX, Inc.
Attn: Patricia Taylor
Senior Director, Regulatory Affairs
981F Industrial Road
San Carlos, CA 94070

Dear Ms. Taylor

Please refer to your Investigational New Drug Application (IND)/New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4)™, capsaicin dermal patch, 8%.

We also refer to the meeting between representatives of your firm and the FDA on March 17, 2006. The purpose of the meeting was to discuss proposed starting material, manufacturing controls, and proposed formulation changes.

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 Karl Stiller, Regulatory Health Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Karl Stiller
Regulatory Health Project Manager
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 17, 2006
TIME: 11:00 am – 12:30 pm
LOCATION: CDER White Oak 1201 Conference Room
APPLICATION: IND 63,354
SPONSOR: NeurogesX, Inc.
DRUG NAME: (b) (4) (capsaicin patch, 8%)
TYPE OF MEETING: Type B CMC Meeting
MEETING CHAIR: Ravi Harapanhalli, PhD
MEETING RECORDER: Karl Stiller

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment Division of Pre-Marketing Assessment III:

Ravi Harapanhalli, PhD., Branch Chief
Christine Moore, PhD., Branch Chief
Ali Al-Hakim, PhD., Pharmaceutical Assessment Lead
Terrance Ocheltree, PhD., Review Chemist
Karl Stiller, Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

NeurogesX

Irina Beylin, Manufacturing
(b) (4) Manufacturing Consultant
Karen J. Harder, Regulatory and Quality
Patricia Taylor, Regulatory
Linne Conrad, Quality Assurance

BACKGROUND:

NeurogesX is developing a capsaicin-containing, dermal patch, (b) (4) proposed for the management of (b) (4) postherpetic neuralgia. NeurogesX requested a Chemistry, Manufacturing and Controls (CMC) meeting, dated January 11, 2006. A Type B meeting was granted with NeurogesX on January 25, 2006, and held on March 17, 2006.

A pre-meeting CMC briefing document dated February 15, 2006 outlining discussion topics and questions was sent by NeurogesX FDA provided written responses to all questions outlined in the briefing document prior to the meeting.

The following are the firm's questions and FDA pre-meeting responses. All of these are related verbatim. Additional discussion immediately follows the respective FDA pre-meeting response.

A. DRUG SUBSTANCE

A.1 Regulatory Starting Materials

Does the Agency concur that [REDACTED] (b) (4) meet the criteria to be considered the Regulatory Starting Materials (RSM) in the capsaicin manufacturing process?

FDA Response-

- [REDACTED] (b) (4)
[REDACTED]
[REDACTED] can be considered as a starting material provided that reasonable justification is provided which includes:
 - Information on commercial availability
 - Whether known in the literature (e.g. Publication and literature related information)
 - Typical synthetic pathways for its synthesis
 - Complete set of test methods and specifications including impurities and degradation products.
 - Validated analytical methods capable of resolving and quantifying impurities carried over from the proposed starting materials in the drug substance and the process impurities that result in the synthesis of the drug substance from the proposed starting materials.
 - Maintenance of purified and well-characterized referenced starting materials.
 - The proposed starting materials, impurities in the proposed starting materials, and the synthetic by-products of the impurities in the proposed starting materials should be not more than 0.1% in the drug substance, provided these are nonstructural alerts for genotoxicity,
 - If any of the above materials are structural alerts for genotoxicity, they may have to be limited to much lower levels than 0.1% or may have to be qualified for lack of genotoxicity.
 - Adequate change controls including vendor qualification and audits and vendor's obligations to report any changes to the synthetic process.
 - All post-approval changes should conform to BAC-PAC 1 guidelines (e.g., Change Controls).

Meeting Discussion A.1: NeurogesX stated that [REDACTED] (b) (4) is a well-characterized compound in the non-pharmaceutical market, so no DMF will be referenced. FDA requested information on proposed [REDACTED] (b) (4) manufacturers.

FDA cautioned [redacted] (b) (4)

NeurogesX agreed to provide information on [redacted] (b) (4) and adequate specifications on its control in the NDA.

NeurogesX asked if the proposed specifications in the briefing package (p. 16) were adequate. FDA stated that the specifications appear to be adequate, but data on purging studies and spiking studies should be submitted in the pharmaceutical development report to demonstrate the process capability of [redacted] (b) (4) and to define acceptable quality for [redacted] (b) (4)

A.2 Regulatory Starting Materials ([redacted] (b) (4))
Does the Agency concur that [redacted] (b) (4) and [redacted] (b) (4) are [redacted] (b) (4)

FDA Response-

- See responses to question 1.

Meeting Discussion A.2: No further discussion.

A.3 [redacted] (b) (4) Specifications
Does the Agency concur that [redacted] (b) (4) and the proposed specification is acceptable to support an NDA filing?

FDA Response-

- In order to consider [redacted] (b) (4), the following supportive information should be provided
 - Structural characterization
 - Complete tests and specifications should be provided
 - Stability profile during holding time
 - Any other pertinent information and controls on its quality

Meeting Discussion A.3: NeurogesX agreed to provide the requested information.

A.4 Manufacturing History and Evolution
NeurogesX requests that the Agency review the [redacted] (b) (4) manufacturing process [redacted] (b) (4)

(b) (4), does the Agency agree that the proposed drug substance specifications are appropriate to support the proposed NDA (b) (4)?

FDA Response-

- The proposed drug substance specifications are satisfactory. However, the limits for impurities may be tightened and/or justified based on the capabilities and experiences gained from the manufacturing process and safety considerations.

Meeting Discussion A.4: NeurogesX, Inc. agreed to follow FDA's recommendations on tightening and/or justifying impurity limits.

A.5 (b) (4)
Does the Agency agree that the evaluation of (b) (4) is adequate and that no further evaluation is needed?

FDA Response-

- Yes, (b) (4)

Meeting Discussion A.5: NeurogesX agreed to provide the experimental data.

A.6 (b) (4)
Does the Agency agree that the current specifications are adequate to control (b) (4) using the current analytical method?

FDA Response-

- Yes.

Meeting Discussion A.6: No further discussion.

B. DRUG PRODUCT: DERMAL PATCH

B.1 Formulation/Method of Manufacturing Process Changes NeurogesX requests that the Agency review the (b) (4) formulation changes (b) (4) made to the patch drug product during development. As no further changes are planned, we ask for concurrence that the testing conducted to support these changes is appropriate to support the commercial process which will be submitted in the NDA.

FDA Response-

- More bridging is required, including permeation studies, to demonstrate that the different products (old vs. improved) perform equally. Has a correlation been established between

in vitro and in vivo permeation?

- It is unclear which formulation (old or improved) was used for clinical studies. Was the change made at the end of phase 2 or during the course of phase 2 studies? Has the new formulation been utilized in any clinical studies?
- The in vitro drug testing (b) (4) is not indicative of dermal delivery as the test occurs over a much longer time period. The media used in the dissolution studies is unclear and warrants more discussion. Provide evidence of correlation between clinical studies and Franz cell permeation studies to demonstrate product performance.
- (b) (4)
- Discussion should be provided whether size and distribution of (b) (4) are considered critical for rate of drug release. If so, adequate controls should be identified.
- Provide detail related to how much drug is delivered or remains in the patch after the proposed wear period and on the skin after cleansing gel treatment.
- (b) (4) have not been used in commercially available transdermal products, toxicological information may be required. This should be discussed with the Pharmacology/Toxicology discipline.
- (b) (4)
?
?
- Adequate stability data for the proposed commercial formulation is expected in the NDA.
- Provide a comparative table on the impurity profiles of the formulations used for pharmtox and clinical studies and that proposed for commercial launch.
- Acceptance specifications for all excipients and materials should be provided including justification for the extent of their control for desirable patch performance. Appropriate acceptance criteria for the adhesives should include viscosity, tackiness, and other attributes reflective of adhesive properties and a justification for the retest periods.

- Specifications must be established for both [REDACTED] (b) (4)
[REDACTED] Release testing should be continued until release has plateaued.

Meeting Discussion B.1:

[REDACTED] (b) (4)
[REDACTED] FDA recommended doing permeation studies showing correlation between the 2 formulations.

Mass balance testing and cadaver skin testing has been performed. FDA asked how much API typically remains on the skin. NeurogesX stated that (b) (4) of the API is delivered to the skin after patch removal and the cleansing gel removes nearly (b) (4) drug from the surface of the skin and (b) (4) is left in the patch.

In Phase 2 testing, the new and old material was used. In Phase 3 testing, the new material was used exclusively.

[REDACTED] (b) (4)
[REDACTED]

FDA noted that testing conditions should be reevaluated. [REDACTED] (b) (4)

[REDACTED]
NeurogesX requested information on testing guidance. FDA suggested that the SUPAC semi-solid guidance may be useful to some extent.

[REDACTED] (b) (4)
[REDACTED]
[REDACTED] FDA stated that the delivery of the API through the adhesive to the skin was not adequately described in the meeting package.

B.2 In Process Controls

In-process controls for the patch drug product have been defined. Does the Agency agree that the IPCs identified are appropriate for the NDA submission?

FDA Response-

- The information provided was not sufficient to adequately determine acceptability.
- Provide test methods and justify for In Process Controls (IPC) sampling plan, including frequency of testing and location of samples, which is representative of commercial

manufacturing scale.

- [REDACTED] (b) (4)
- In-process content uniformity testing should be continued routinely and the sampling plan should be representative of the manufacturing process [REDACTED] (b) (4). Upon demonstrating adequate process capability, these tests may be reassessed.
- Viscosity may be a critical parameter that needs to be monitored [REDACTED] (b) (4).

Meeting Discussion B.2: NeurogesX asked if the stratified sampling described was adequate, and asked for clarification about the FDA response pertaining to viscosity sampling. FDA requested data on 3 validation batches and for the stratified sampling. With regard to viscosity sampling, sampling criteria should be developed to determine consistency of viscosity between batches before [REDACTED] (b) (4).

B.3 Specifications

Does the Agency agree that the proposed specifications are adequate for [REDACTED] (b) (4)™ (capsaicin patch, 8%)?

FDA Response-

- [REDACTED] (b) (4) testing should be performed.
- Justify adequacy of peel force testing.
- Provide data on [REDACTED] (b) (4) on release and stability.
- Range of patch size (+/- the target size) is needed in the spec.
- Adequate instructions for use should be included in the clinical package including hygiene precautions for safe handling.
- The background package indicates that the patches are to be cut. How is adhesive

performance and stability affected by opened packages and cut patches?

- [REDACTED] (b) (4)
[REDACTED] ?

Meeting Discussion B.3: [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

C. DRUG PRODUCT: CLEANSING GEL

C.1 [REDACTED] (b) (4)
During product development, [REDACTED] (b) (4) changes have been made to the Cleansing Gel [REDACTED] (b) (4). As no further changes are planned to the [REDACTED] (b) (4) composition, does the agency agree that the information provided is sufficient to support an approvable NDA?

FDA Response-

- Provide details related to IPC [REDACTED] (b) (4)
- Antimicrobial preservative effectiveness should be demonstrated throughout the shelf life of the product and Antimicrobial Effectiveness Test included in stability testing until greater knowledge of the product is gained.
- Extractable and leachables are required for the container closure system.

See comments for functionality test.

Meeting Discussion C.1: FDA stated that anti-microbial preservative (APE) effectiveness testing and microbial limit testing should be carried out to justify expiry dating period. NeurogesX asked if APE testing would be adequate. FDA stated that APE testing should include time-0 and end of expiry date time points, but microbial limit testing is still recommended.

C.2 (b) (4)

(b) (4)

FDA Response-

- The purpose of the cleansing gel should be addressed. How critical is removal of capsaicin after patch removal? Is it critical to drug delivery, safety, or patient comfort? The proposed testing is not appropriate due to lack of information regarding the capacity of the gel to remove capsaicin and adhesive.
- (b) (4)
- Clinical data may be required to demonstrate gel effectiveness.

Meeting Discussion C.2: (b) (4)
(b) (4). Solubility of capsaicin in the cleansing gel is (b) (4), and (b) (4) of the capsaicin left on the skin surface is removed by the cleansing gel. No problems with capsaicin contamination (transfer) have been reported. No adverse event reports have been related to the use of the gel. Clinical data is being collected to demonstrate gel effectiveness in removing capsaicin. The Agency agreed with this approach and requested that the summary of the data be made available in the NDA.

D. DEMONSTRATION PATCH: PLACEBO PATCH

D.1 Formulation/Method of Manufacturing and Specifications

NeurogesX plans to manufacture a demonstration patch which will be supplied to physicians and used to demonstrate the correct application and removal of a dermal patch dosage form to patients. Placebo patches are formulated (without capsaicin) and manufactured to be identical in appearance to (b) (4)™ (capsaicin patch, 8%). A separate drug product section of the NDA CMC section will describe all appropriate aspects of manufacturing and testing. Does the Agency agree that the criteria for the approval of the placebo demonstration patch can be based on the information identified in this amendment to the IND? Does the agency concur that one lot of placebo demonstration product is sufficient for an NDA filing?

FDA Response-

- IPC and specifications, including sampling should be representative of the manufacturing

process.

- Specifications for [REDACTED] ^{(b) (4)} should be established based on toxicology.
- Comparison of Placebo and proposed commercial formulation should be performed to ensure similar short term and long term performance.

Meeting Discussion D.1: NeurogesX stated that 1 demonstration patch batch will be put on stability, and data on 3 batches containing API will be tested and included in the NDA. FDA agreed with limiting the demonstration patch testing to a single batch.

NeurogesX asked whether the demonstration patch will require a separate NDC number. FDA stated that the question would be looked into, although, it appeared that a separate NDC number may not be needed.

Minutes Preparer: _____

Karl Stiller
Regulatory Health Project Manager
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment

Chair Concurrence: _____

Ravi Harapanhalli, PhD
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment

13 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

Ravi Harapanhalli
4/18/2006 05:29:05 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63,354

NeurogesX, Inc
981F Industrial Road
San Carlos, CA 94070

Attention: Karen J. Harder
Senior Vice President of Regulatory Affairs and Technical Operations

Dear Ms. Harder:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b)/505(i) of the Federal Food, Drug, and Cosmetic Act for [REDACTED]^{(b) (4)} (capsaicin patch, 8%).

We also refer to the meeting between representatives of your firm and the FDA on October 26, 2005. The purpose of the meeting was to discuss issues related to the development of a capsaicin dermal patch [REDACTED]^{(b) (4)}

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

If you have any questions, call me at (301) 796-1251.

Sincerely,

{See appended electronic signature page}

Lisa Malandro
Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 26, 2005
TIME: 11:30 am
LOCATION: White Oak, Conference room 1537
APPLICATION: IND 63,354
DRUG NAME: Capsaicin Dermal Patch
INDICATION: (b) (4)
TYPE OF MEETING: EOP2

MEETING CHAIR: Mwango Kashoki, MD, MPH

MEETING RECORDER: Lisa Malandro

FDA Attendees:

- Bob Rappaport, MD, Division Director
- Curtis Rosebraugh, MD, MPH, Deputy Director of ODE II
- Mwango A. Kashoki, MD, MPH, Acting Medical Team Leader
- Thomas Permutt, Ph.D, Team Leader Statistics
- Suzanne Thornton-Jones, PhD Pharm/Tox
- David Lee, Biopharmaceutics
- Ellen Fields, MD Medical Officer
- Lisa Marie Malandro, Regulatory Project Manager
- Carol Ann Currier, DSI (via telephone)
- Sandy Birdsong, Chief Project Management ODS
- Kendall Marcus, MD, Division of Antiviral Products
- Nevill Gibbs, MD, Division of Antiviral Products

NeurogesX Attendees:

- John A. Jermano, RN, MPH, Clinical Development
- (b) (4) (Clinical Consultant)
- Stephen Chang, PhD, Biostatistics
- Sanjay Chanda, PhD, Toxicology
- Irina Beylin, Pharmaceutical Sciences
- Patricia Taylor, Regulatory
- Karen J. Harder, Regulatory and Quality

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/s/

Lisa Malandro
1/24/2006 11:49:28 AM



IND 63,354

NeurogesX, Inc.
San Carlos Business Park
981F Industrial Road
San Carlos, CA 94070-4117

Attention: Karen J. Harder
Vice President, Regulatory Affairs

Dear Ms. Harder:

Please refer to the meeting between representatives of your firm and FDA on March 6, 2003. The purpose of the meeting was to reach concurrence on the design of the upcoming well-controlled studies, including the selection of the efficacy endpoint and an appropriate control; to reach concurrence on the need to conduct reproductive toxicology studies; to reach concurrence on the plan for additional genotoxicity testing and, if carcinogenicity is required, on the appropriate carcinogenicity animal model; and to reach concurrence on the design of an NDA-enabling stability program for the drug product..

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

If you have any questions, call me at (301) 827-7407.

Sincerely,

{See appended electronic signature page}

Lisa Marie Malandro
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Meeting Date: March 6, 2003

Time: 1:30 PM

Location: Parklawn Building, Conference Room C

Drug: Capsaicin Dermal Patch

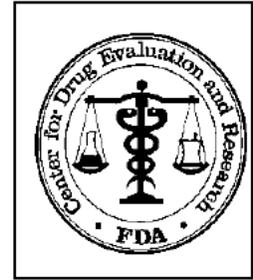
Sponsor: NeurogesX

Indication: Dermal analgesic for neuropathic pain

Type of Meeting: End-of-Phase 1

Meeting Chair: Sharon Hertz, M.D., Medical Team Leader

Minutes Recorder: Lisa M. Malandro, Regulatory Project Manager



NeurogesX, Inc. Attendees	Title
Thorsten von Stein, MD, PhD	Clinical Development
(b) (4)	Consulting Biostatistician
Sanjay Chandra, PhD	Nonclinical Toxicology
Gene Jamieson	Pharmaceutical Sciences
Karen Harder	Regulatory and Quality
John Jermano	Clinical
Meredith Brown	Regulatory
FDA Attendees	Title
Bob Rappaport, M.D.	Acting Division Director
Sharon Hertz, M.D.	Medical Team Leader
Dale Koble, Ph.D.	Chemistry Team Leader
Tim McGovern, PhD	Team Leader, Pharmacology/Toxicology
D. Elizabeth McNeil, MD	Medical Officer
Michael Theodorakis, PhD	Chemistry Reviewer
David Lee, PhD	Biopharmacology Reviewer
Stella Grosser, PhD	Statistics Reviewer
Lisa M. Malandro	Regulatory Project Manager

Meeting Objectives: To reach concurrence on the design of the upcoming well-controlled studies, including the selection of the efficacy endpoint and an appropriate control; to reach concurrence on the need to conduct reproductive toxicology studies; to reach concurrence on the plan for additional genotoxicity testing and, if carcinogenicity is required, on the appropriate carcinogenicity animal model; and to reach concurrence on the design of an NDA-enabling stability program for the drug product.

General Discussion: Following introductions, the discussion focused on the sponsor's questions that were included in the February 5, 2003, meeting package. The sponsor's questions are listed in italics and the Division's responses in regular font. Discussion occurring at the meeting is in the appropriate context.

1. Does the Agency concur that the manufacturing and stability plans proposed for the drug product and non-drug containing cleansing gel are appropriate and adequate to support an acceptable NDA?

- Drug substance: Capsaicin (submission dated September 24, 2002)
 - a. Identify and qualify impurities as per ICH guideline.
 - b. In the specification sheet identify what are the solvents under the heading "other organic solvents".
- Drug product: Capsaicin Dermal Patch (submission dated September 24, 2002)
 - a. Provide the grade of the ingredients used in the Capsaicin Dermal Patch
 - b. The shelf-life specifications should be revised to include degradation products, and (b) (4) content.
 - c. Identify and qualify degradation products as per ICH guidelines.
 - d. Provide stability data on three batches of the dermal patch as per FDA/ICH guidelines.
- Your proposal to submit 12-month data for a (b) (4) patch batch and six-month data for (b) (4) - patch batch, as well as the 2-year data from the pilot batches is acceptable. For pilot batches we will accept the two (b) (4) patch batches.
- Cleansing gel (submission dated July 10, 2002)
 - a. Provide stability data on three batches of the reformulated gel as per FDA/ICH guidelines.
 - b. Provide specifications for viscosity and pH.
 - c. Test for assay for individual ingredients in the cleansing gel.
 - d. Identify and qualify degradation products, if any.

Discussion:

The Division stated that if the packaging is permeable, the ICH guidelines for low relative humidity should be addressed. The Division also stated that performance testing is required for the cleansing gel. The Sponsor should ascertain that the cleansing gel has the same performance over two years. All excipients in the cleansing gel should be assayed. In the absence of performance testing, justification as to why the Sponsor feels this is not necessary should be provided.

- Provide a written justification for the proposed tests, test methods, and acceptance criteria for the drug substance and drug product with reference to appropriate supporting data.

2. *In a recently completed clinical study, there was no detectable systemic exposure to capsaicin following topical application of the Capsaicin Dermal Patch. In addition, there is epidemiological evidence that dietary capsaicin is not a reproductive toxicant. Given this information, does the Agency concur that no reproductive toxicology studies will be required for an acceptable NDA?*
- Reproductive toxicology studies may be waived if:
 - an absence of systemic exposure to capsaicin and metabolites is adequately demonstrated in ongoing/future clinical trials,
 - an in silico assessment is provided and is negative, and
 - a written safety assessment concerning the risk associated with the level of detection versus exposure information for known reproductive toxicants is provided

Discussion:

[REDACTED] (b) (4)

3. *Does the Agency concur that the genotoxicity proposal presented is an appropriate approach in determining if a waiver of carcinogenicity studies can be granted for an acceptable NDA?*
- No. Negative results in the proposed assay will not offset previous positive findings.
 - However, demonstration of no clinical systemic exposure (similar to that described previously) and/or an expected clinical use of < 3 months duration or a highly infrequent use could support a waiver of carcinogenicity studies.

Discussion:

The Sponsor asked for clarification of “chronic use.” The Division explained that the guidelines defined chronic use as a compound that is used for 6 months or longer, including intermittent use equalling a total period of six months or longer over a lifetime. Highly infrequent use is generally regarded as less than 6 months of use over a lifetime. [REDACTED] (b) (4)

[REDACTED] The Division stated that the evaluation of the clinical studies will determine this. ICH Guidance S1A states that for pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed. The Division clarified that even if the genotoxicity battery has no findings, carcinogenicity studies are necessary if the drug will be used chronically.

- Positive genotoxicity findings with capsaicin should be described in the Investigator Brochure and Informed Consent in an unbiased manner.

Additional non-clinical comments:

- Lack of significant systemic exposure in two animal species using dermal application may warrant further toxicologic assessment via alternate routes in the presence of clinical exposure to support clinical trials.

Discussion:

The Division stated that, if there is systemic exposure during the clinical trials, additional animal data will be required (i.e., systemic exposure in two animal species). The Sponsor questioned if their current data is sufficient providing that there is no systemic exposure in humans. The Division stated that the current data is sufficient to support clinical trials, but may not be sufficient to support a marketing claim. In the event of potential systemic exposure, the Division requires that an attempt be made to understand potential toxicities. The Division acknowledged the toxicity seen in the rat data and stated that toxicity in a non-rodent species, perhaps by an alternative dose administration, would be required.

- Regardless of clinical exposure, characterization of potential toxicity profile should be performed, possibly via alternate route.
- ICH Guidance for Industry M3 should be referenced for duration of toxicity studies to support marketing.
 - repeat dose studies in 2 species (at least 1 non-rodent) of at least 1 month duration will be needed.
 - this requirement could be waived should a lack of clinical exposure be adequately demonstrated.
- The current specification of (b) (4) does not appear to be adequately qualified for safety
 - safety margins of < 1 to 4-fold based on body weight and body surface area comparisons
- The specification for capsaicin should be reduced or adequate safety qualification should be provided to support future clinical trials.
- The metabolic profile of capsaicin following dermal administration should be fully characterized.

Discussion:

(b) (4)

The Sponsor questioned if this should be studied *in vitro*. The Division stated that an *in vivo* study is best since *in vitro* studies are not always equivalent. However *in vitro* studies may serve as a starting point for *in vivo* studies. Following the *in vitro* studies, the data should be evaluated to determine if additional studies are required. The Sponsor questioned if liver microsome studies would be acceptable since skin cells are difficult to maintain. The Division stated that studies using liver microsomes are acceptable as an *in vitro* model. *In vitro* studies should be followed up with appropriate *in vivo* assessment.

The Division also stated that metabolic profiling data is required for humans. The Sponsor questioned what would be a suitable assay. The Division suggested use of separate species are easily measured by radioactivity counting methods.

- Impurities exceeding ICH recommended levels should be adequately qualified for a marketing application.

4. *Is the data to be collected as the primary efficacy endpoint outlined in the appended adequate and well-controlled study synopses appropriate to support an acceptable New Drug Application (NDA)?*
 - In order to address duration of effect in treatment of the chronic pain of PHN, the change from baseline to the end of the study is important. The chosen primary efficacy endpoint is acceptable.

5. *NeurogesX' understanding of previous statements by FDA representatives is that 12-week efficacy is required as the primary endpoint in neuropathic pain studies. This requirement is the basis for the design of the pivotal studies presented here. However, would the Agency also consider a primary efficacy endpoint definition based only on the first 8 weeks with the understanding that subjects would be followed in a blinded fashion over 12 weeks?*
 - We would be willing to accept an eight week trial for the PHN indication.

Discussion:

[REDACTED] (b) (4)

The Sponsor stated that they are currently planning 12-week trials focusing on determining the efficacy of the product and characterizing the duration of the effect. The Division stated that the dosing regimen for this product is very unique and that there are still some outstanding questions (such as how long does it take to work, how often is re-application necessary, etc) which the Sponsor will need to answer. The Division asked how the Sponsor planned on capturing the duration of efficacy and how often reapplication should take place. The Sponsor stated that they plan to collect daily pain scores to help determine the duration of pain relief. Decisions will be made by the individual investigators after the initial study period. The Division clarified that while the change from baseline to the end of the study is important, if AUC analysis demonstrates that the bulk of the improvement occurs early in the treatment period, this will modify recommendations about the appropriate dosing interval.

Post meeting addendum:

Upon reconsideration of the unique nature of this [REDACTED] (b) (4), the following recommendations are made:

1. The duration of effect from a single application should be determined.
2. Based on the information about the duration of effect, a study should be designed to explore the appropriate dosing interval for this product.
3. Pivotal efficacy data should be obtained from a study demonstrating efficacy over a minimum of an 8 week period using the dosing interval identified as noted above.

6. *Since the use of a traditional placebo arm will not permit studies to remain blinded, does the Agency concur that a low-concentration dermal patch, with no anticipated efficacy, is an appropriate control arm for the conduct of adequate and well-controlled trials? Data from NeurogesX clinical studies C102 (lack of efficacy in the clinical setting) and C101 (mechanism of action) support lack of efficacy in the low-concentration dermal patch.*
 - Yes.

7. *The appended dose-finding studies use patch exposure time as the dosing variable, not patch concentration. Are the designs of study C108 in postherpetic neuralgia (PHN) [REDACTED] (b) (4) [REDACTED] adequate to generate data to define an appropriate patch exposure time, and thus establish a recommended labeled dose?*
- The overall study design is appropriate.
 - The pooled analysis will not be acceptable.

Discussion:

[REDACTED] (b) (4)

The Sponsor stated that they would modify their analysis procedures.

[REDACTED] (b) (4)

The Division also stated that the dosing duration may dictate the efficacy endpoint. The Division expressed their concerns about the unknown exposure and reminded the Sponsor that they should attempt to identify the optimal dose exposure [REDACTED] (b) (4)

[REDACTED] (b) (4)

The Division stated that bioequivalence studies would be difficult to design for this product, so the Sponsor should be sure that their to-be-marketed formulation is completed prior to beginning their clinical studies.

8. *In addition to the primary pain assessment using patient-reported intensity scores, other efficacy-related assessments such as the McGill questionnaire and patient global assessment of change will be done. In absence of a validated instrument to capture functional status and Quality of Life in neuropathic pain patients, NeurogesX plans to include the Brief Pain Inventory (BPI). Does the Agency concur that failure to demonstrate differences in these assessments will not negate findings of statistically significant improvement in the primary efficacy variable (pain)?*

- We concur. A finding of analgesic efficacy does not require a demonstration of improvement in function or quality of life.
- We encourage measurement of function and quality of life using validated assessment tools to ensure that these outcomes do not worsen during the clinical trial.
- We would recommend use of rescue medication as a secondary outcome measure.

Discussion:

The Division clarified that the use of rescue medication and concomitant analgesics would be expected to decrease or remain stable over the study period. If the patients required more rescue medication or upward titration of concomitant analgesics, it would appear that the analgesic effects of the capsaicin dermal patch were waning. The Division also clarified that while enrolling patients who are currently using stable chronic analgesics is acceptable, if the majority of study patients were using a particular class of medication, that information might be included in the label.

The Sponsor asked if the Division could recommend a validated tool for assessing neuropathic pain. The Division suggested that the Sponsor evaluate what the community uses to assess postherpetic neuralgia and provide justification for its use.

9. *The statistical analysis plans for the two adequate and well-controlled studies discussed are outlined in Section 5 of this package. Does the Agency concur that the statistical plans as outlined are adequate and appropriate to support an acceptable NDA, particularly with respect to hypothesis testing and interim futility analysis?*

- The statistical plans are acceptable.
- The hierarchical testing procedure in C108 may need to be reconsidered, (b) (4)
- Please provide details on the interim futility analysis, particularly stopping criteria.

Discussion:

The Division encouraged the Sponsor to consider a responder- analysis. The Division stated that this type of analysis would allow the Sponsor to use the data from the 90-minute group since those who do not tolerate the 90-minute dose would count as failures. Since there is not a generally accepted method for this type of analysis, it was agreed that these analyses would be exploratory. The Sponsor stated that they are willing to add this type of analysis as a secondary endpoint.

10. *Statistical plans for the proposed studies outline the intention to conduct the primary analysis after all subjects have been observed for 12 weeks following treatment, with an addendum analysis planned to add long-term follow-up data. Does the Agency concur that study reports of the primary analysis would be appropriate to support an acceptable NDA?*

- The primary analysis based on results from the end of the double-blind 12 (or 8) week treatment period are appropriate to support a finding of efficacy.
- An open-label extension for additional safety information is also appropriate.

11. *As no systemic exposure was measurable in the completed clinical study (C102 in PHN), does the Agency concur that a formal study of the pharmacokinetics of capsaicin, administered as a dermal patch, is not needed for an acceptable NDA in PHN? Does the Agency further agree that*

similar capsaicin plasma level data, generated in other indications, would make pharmacokinetic studies in those patients unnecessary?

- Additional information from Study C102 is needed :
 -  (b) (4)
 - 
 - 
- Overall, the capsaicin systemic exposure information using the maximum likely clinical dosage [e.g., total applied surface area, repeat administration (C108 - 3 treatments with 12 wk washout, etc.) is needed. If capsaicin can be detected systemically after maximum application, a comprehensive capsaicin characterization is needed.
- Yes, pending adequate information stated above is obtained.

Discussion:

The Sponsor provided the following response to the Division's questions (above):  (b) (4)



The meeting adjourned at 3:00 pm

Minutes prepared by: Lisa M. Malandro

Minutes concurred by Chair: Sharon Hertz, M.D.

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/s/

Lisa Malandro
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