

*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/cm<sup>2</sup>)

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

*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.*

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**1. GENERAL**

a. United States Patent Number

6,248,788

b. Issue Date of Patent

June 19, 2001

c. Expiration Date of Patent

November 6, 2016

d. Name of Patent Owner

The Regents of the University of California

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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

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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

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

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## 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

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

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

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

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

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

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

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

Investigation #1 !

YES

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.**

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/s/

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TANYA D CLAYTON  
11/16/2009

BOB A RAPPAPORT  
11/16/2009

**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 <sup>1</sup>		
NDA # 22-395 BLA #	NDA Supplement # BLA SFN #	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</u>s:</p> <p>NDA Application Type:   <input type="checkbox"/> 505(b)(1)   <input checked="" type="checkbox"/> 505(b)(2)</p> <p>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></p> <p>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.</p> <p>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><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input checked="" type="checkbox"/> No changes                      <input type="checkbox"/> Updated Date of check: July 8, 2009; October 23, 2009</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>	
❖ User Fee Goal Date Action Goal Date (if different)	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	

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

❖ 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 <sup>2</sup> 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) <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">http://www.fda.gov/ora/compliance_ref/aip_page.html</a>	
• 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

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

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and 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></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>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></li> </ul>	<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"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

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

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

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

Yes       No

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

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

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

Yes       No

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

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

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

Yes       No

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

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

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

Yes       No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
<b>CONTENTS OF ACTION PACKAGE</b>	
<p>❖ Copy of this Action Package Checklist<sup>3</sup> In</p>	<p>cluded</p>
<b>Officer/Employee List</b>	
<p>❖ 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>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/nonconsent by officers/employees</p>	<p><input type="checkbox"/> Included</p>
<b>Action Letters</b>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) November 16, 2009</p>
<b>Labeling</b>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<p>❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</p>	<p>November 16, 2009</p>
<p>❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</p>	<p>N/A</p>
<p>❖ Original applicant-proposed labeling</p>	<p>N/A</p>
<p>❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</p>	<p>N/A</p>
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<p><input type="checkbox"/> Medication Guide  <input type="checkbox"/> Patient Package Insert  <input type="checkbox"/> Instructions for Use  <input checked="" type="checkbox"/> None</p>
<p>❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</p>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
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❖ 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 ( <b>full color</b> 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
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/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"> <li>• Center Director's Exception for Review memo</li> <li>• If approval action, OC clearance for approval</li> </ul>	<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"> <li>• Outgoing communications (<i>if located elsewhere in package, state where located</i>)</li> <li>• Incoming submissions/communications</li> </ul>	<input checked="" type="checkbox"/> None
❖ Postmarketing Commitment (PMC) Studies <ul style="list-style-type: none"> <li>• Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>)</li> <li>• Incoming submission documenting commitment</li> </ul>	<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	

<sup>4</sup> Filing reviews for other disciplines should be filed behind the discipline tab.  
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• 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	
<b>Decisional and Summary Memos</b>	
❖ 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
<b>Clinical Information<sup>5</sup></b>	
❖ 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
<b>Clinical Microbiology</b> <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
<b>Biostatistics</b> <input type="checkbox"/> None	

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
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❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None July 1, 2009
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None July 7, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None July 17, 2009
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None July 17, 2009
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None July 17, 2009; Oct. 27, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<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
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Nov. 6. 2009
• Branch Chief/TeamLeader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None May 14, 2009; July 1, 2009; September 15, 2009
• BLAs only: Facility information review(s) ( <i>indicate dates</i> )	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	CMC Review #1, page 121, May 14, 2009
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	

<ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)</li> </ul>	<p>Date completed:</p> <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> <li>• BLAs:             <ul style="list-style-type: none"> <li>➤ TBP-EER</li> <li>➤ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>)</li> </ul> </li> </ul>	<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"> <li>❖ NDAs: Methods Validation</li> </ul>	<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

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/s/

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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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SARA E STRADLEY  
08/05/2009



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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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.<sup>1</sup> 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

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<sup>1</sup> 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)<sup>2</sup>. 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

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<sup>2</sup> 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
<b>Number of Patients</b>	229	129	44
<b>Immediately After Patch Removal</b>	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)
<b>1-2 Hours After Patch Removal</b>	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)
<b>Maximum Score On Day 0[1]</b>	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).<sup>3</sup>

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

**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)
<b>Maximum Score on Day 0, n (%)</b>				
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
<b>Maximum Increase <math>\geq</math> 2 Points, n (%)</b>				
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 cm<sup>2</sup> 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<sup>4, 5, 6, 7</sup> 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

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<sup>4</sup> 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

<sup>5</sup> 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.

<sup>6</sup> 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.

<sup>7</sup> 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 cm<sup>2</sup> 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 cm<sup>2</sup> 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

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/s/

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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

**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

**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
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?

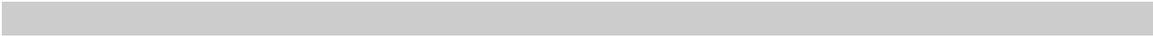
YES  NO

*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

**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

## REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Dermatology and Dental Products/ Margo Owens, Team Leader, HFD-540**

FROM (Name, Office/Division, and Phone Number of Requestor): **HFD-170, Division of Anesthesia, Analgesia, and Rheumatology Products  
Tanya Clayton**

DATE  
**April 24, 2009**

IND NO.

NDA NO.  
**22-395**

TYPE OF DOCUMENT  
**NDA**

DATE OF DOCUMENT  
**October 13, 2008**

NAME OF DRUG  
**Capsaicin Patch 8%**

PRIORITY CONSIDERATION  
**High**

CLASSIFICATION OF DRUG  
**2040200/Neuropathic Pain**

DESIRED COMPLETION DATE  
**June 5, 2009**

NAME OF FIRM: **Neurogesx, Inc.**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** The sponsor asserts that since the proposed Prescribing Information contains adequate warnings and information regarding the neurogenic inflammation/irritation caused by NGX-4010, the applicant NeurogesX believes these studies should be waived. The sponsor has provided additional arguments for waiving all the Dermal Safety Studies in the attached document.

The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) requests the expertise of the Division of Dermatology and Dental Products (DDDP) to address the following questions.

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 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 pretreatment. 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 those 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 document: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products, still current or is it considered obsolete at this time?

cc: Applicant's rationale for waiver request  
Proposed product label are attached.

The PDUFA date for this NDA is August 16, 2009.

If you need additional information please contact the RPM, Tanya Clayton at 60871 or MO, Neville Gibbs at 60718.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

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Tanya Clayton  
4/24/2009 12:13:26 PM

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/cm<sup>2</sup> 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 <sup>2</sup> )	0	0.16	0.32	0.64 0		1.56 µg/cm <sup>2</sup> /twice weekly; 3.25 µg/cm <sup>2</sup> /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.AC led 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 M		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 <sup>a</sup>	17 <sup>a</sup>	0	1
Papillomas Combined Sexes		0	2		6		3	0			38 <sup>a</sup>	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 <sup>b</sup>	10 <sup>b</sup>	6	5
Papillomas Combined Sexes		5	3		9		11	7			40 <sup>b</sup>	11		

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

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

<sup>b</sup> 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:\n  
/Division File, DAARP  
/AWasserman, Team leader, DAARP  
/LSLeshin, Reviewer, DAARP  
/TClayton, CSO/PM, DAARP  
/ASeifried, OND IO

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

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

## REQUEST FOR CONSULTATION

TO (Office/Division): Rosemary Addy/George Greeley,  
Pediatric and Maternal Health Staff

FROM (Name, Office/Division, and Phone Number of Requestor): Tanya Clayton, Division of Anesthesia, Analgesia & Rheumatology Products

DATE  
February 3, 2009

IND NO.

NDA NO.  
22-395

TYPE OF DOCUMENT  
Pediatric Plan

DATE OF DOCUMENT  
October 16, 2008

NAME OF DRUG  
Capsaicin Patch 8%

PRIORITY CONSIDERATION  
Normal

CLASSIFICATION OF DRUG  
Pain

DESIRED COMPLETION DATE  
July 1, 2009

NAME OF FIRM: NeurogexX, Inc.

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** Along with their NDA, the sponsor submitted their proposed pediatric waiver for birth to 16 years (attached). Please review and provide a meeting date for PERC. The PDUFA goal date is August 16, 2009.

The PM contact is Tanya Clayton, 60871 and the Clinical Reviewer is Neville Gibbs, 60718.

SIGNATURE OF REQUESTOR

Tanya D. Clayton

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

**1.9.1 REQUEST FOR WAIVER OF PEDIATRIC STUDIES**

Product \_\_\_\_\_ name: NGX-4010

NDA \_\_\_\_\_ number: 22-395

Applicant \_\_\_\_\_: NeurogesX, Inc.

Indication: Prolonged Reduction of Neuropathic Pain Associated with Postherpetic Neuralgia (PHN)

1. This waiver request is for the whole pediatric population including patients' age birth to 16 years.
2. The reason for waiving pediatric assessment requirements is that the incidence of PHN in this age group is extremely low and NGX-4010 is therefore not likely to be used in a substantial number of patients.
3. Postherpetic neuralgia, defined as the persistence of pain more than three months after the onset of rash, is a chronic neuropathic pain disorder that develops in some individuals after an acute episode of herpes zoster infection, commonly known as shingles. It is associated with chronic infection of the dorsal root ganglia and nerves caused by reactivation of varicella zoster virus. 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 ~35% in those over the age of 80 years [Opstelten et al. 2001]. Risk factors for developing PHN include old age, severity of pain in acute phase, severity of rash, sensory dysfunction in the affected dermatome(s) during acute phase, magnitude of the humoral and cell-mediated immune response during acute phase, painful prodrome, and fever greater than 38°C during acute phase [Dworkin and Portenoy 1996]. 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].
4. The Applicant certifies that the justification provided in support of the waiver request is valid and in accordance with the requirements of the Pediatric Research Equity Act (PREA).

**Please note:** 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. The Orphan Drug Request further supports an FDA decision to grant NeurogesX a waiver for pediatric studies for NGX-4010.

**REFERENCES**

Dworkin RH, Portenoy RK. Pain and its persistence in herpes zoster. *Pain* 1996;67:241–251.

Guess HA et al. *Pediatrics*. Epidemiology of herpes zoster in children and adolescents: a population-based study. 1985 Oct;76(4):512-7

Hope-Simpson RE. Herpes Zoster in General Practice - Postherpetic Neuralgia. Postherpetic neuralgia. *J.R. Coll. Gen. Pract.*, 25:571-575, 1975.

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Opstelten W, et al. Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. *Fam Pract*. 2002 Oct;19(5):471-5

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Rogers R and Tindall J. Herpes zoster in children. *Arch.Dermatol*, 106:2, 204-207, 1972

Watson C. The medical treatment of PHN: antidepressants, anticonvulsants, opioids and practical guidelines for management. *Herpes Zoster and Postherpetic Neuralgia*, 2<sup>nd</sup> ed. Pain Research and Clinical Management series, 11:39-51, 2001.

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/s/

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Tanya Clayton  
2/3/2009 05:18:50 PM

## REQUEST FOR CONSULTATION

TO (Division/Office):

**Mail: OSE/DMETS, White Oak Bldg. 22**

FROM: HFD-170, Division of Anesthesia, Analgesia, and  
Rheumatology Products

Tanya Clayton

DATE February 9, 2009	IND NO.	NDA NO. 22-395	TYPE OF DOCUMENT Proprietary Name Review	DATE OF DOCUMENT July 16, 2008
NAME OF DRUG Capsaicin Patch 8%		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Pain	DESIRED COMPLETION DATE May 9, 2009

NAME OF FIRM: Neurogesx, Inc.

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE--NDA MEETING        | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER               |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                      |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                           |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                 |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                          |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Tradename |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- |  |   |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES      | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW         | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):  |   |

#### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

#### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

#### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the proprietary names for capsaicin patch, 8%, NDA 22-395. The sponsor is proposing 1. Qutenza and 2. (b) (4) All labeling is available in the EDR at [\CDSESUB1\EVSPROD\NDA022395\0000](#)

The tradename review for (b) (4) was submitted December 4, 2007 and no final review was provided.

**Note: This tradename review was submitted in July under the IND (63,354). All labeling is within the NDA EDR. The IND jacket will only be provided for reference.**

If you have any questions, please contact Tanya Clayton at 301-796-0871.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

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Tanya Clayton  
2/9/2009 04:20:42 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Office/Division): DDMAC/Askine, Mark W		FROM (Name, Office/Division, and Phone Number of Requestor): Tanya Clayton, Project Manager, DAARP		
DATE February 11, 2009	IND NO.	NDA NO. 22395	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT October 16,2008
NAME OF DRUG Capsaicin Patch		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Pain	DESIRED COMPLETION DATE June 1, 2009
NAME OF FIRM: Neurogesx				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL	<input type="checkbox"/> PRE-NDA MEETING	<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER		
<input type="checkbox"/> PROGRESS REPORT	<input type="checkbox"/> END-OF-PHASE 2a MEETING	<input type="checkbox"/> FINAL PRINTED LABELING		
<input type="checkbox"/> NEW CORRESPONDENCE	<input type="checkbox"/> END-OF-PHASE 2 MEETING	<input type="checkbox"/> LABELING REVISION		
<input type="checkbox"/> DRUG ADVERTISING	<input type="checkbox"/> RESUBMISSION	<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE		
<input type="checkbox"/> ADVERSE REACTION REPORT	<input type="checkbox"/> SAFETY / EFFICACY	<input type="checkbox"/> FORMULATIVE REVIEW		
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION	<input type="checkbox"/> PAPER NDA	<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):		
<input type="checkbox"/> MEETING PLANNED BY	<input type="checkbox"/> CONTROL SUPPLEMENT			
<b>II. BIOMETRICS</b>				
<input type="checkbox"/> PRIORITY P NDA REVIEW		<input type="checkbox"/> CHEMISTRY REVIEW		
<input type="checkbox"/> END-OF-PHASE 2 MEETING		<input type="checkbox"/> PHARMACOLOGY		
<input type="checkbox"/> CONTROLLED STUDIES		<input type="checkbox"/> BIOPHARMACEUTICS		
<input type="checkbox"/> PROTOCOL REVIEW		<input type="checkbox"/> OTHER (SPECIFY BELOW):		
<input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE		
<input type="checkbox"/> BIOAVAILABILTY STUDIES		<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS		
<input type="checkbox"/> PHASE 4 STUDIES		<input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG SAFETY</b>				
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY		
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES		<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE		
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)		<input type="checkbox"/> POISON RISK ANALYSIS		
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP				
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> NONCLINICAL		
<p><b>COMMENTS / SPECIAL INSTRUCTIONS:</b> NDA 22-395 was submitted October 16, 2008. The proposed indication is the management of neuropathic pain in patients with postherpetci neuralgia. The sponsor has submitted proposed labeling along with the application. Please review and provide comments.</p> <p>The labeling is fully electronic and can be located within the EDR under \\CDSESUB1\EVSPROD\NDA022395\0000.</p> <p>Please contact me at 60871 if you need further information.</p>				
SIGNATURE OF REQUESTOR Tanya Clayton		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER		

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Tanya Clayton  
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Mail: OSE/DMETS, White Oak Bldg. 22</b>		FROM: HFD-170, Division of Anesthesia, Analgesia, and Rheumatology Products Tanya Clayton		
DATE 12/31/08	IND NO.	NDA NO. 22-395	TYPE OF DOCUMENT Labeling	DATE OF DOCUMENT 10/13/08
NAME OF DRUG Capsaicin Patch 8%		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Pain	DESIRED COMPLETION DATE 3/31/09
NAME OF FIRM: Neurogesx, Inc.				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Carton and Container labeling				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS:				
<p>Please review the carton and container labels and package insert for the NDA 22-395 from 10/13/08. This is an electronic submission. <a href="#">\CDSESUB1\EVSPROD\NDA022395\0000</a></p> <p><b>Note: Per Kellie Taylor, Cathy Miller will be the reviewer for this consult.</b></p> <p>If you have any questions, please contact Tanya Clayton at 301-796-0871.</p>				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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Tanya Clayton  
12/31/2008 01:16:51 PM

## REQUEST FOR CONSULTATION

TO (Office/Division): Office of Biometrics, Yi Tsong, Ph.D.

FROM (Name, Office/Division, and Phone Number of Requestor): Theodore Carver/Danae Christodoulou, Division of Pre-Marketing Assessment I, Off. of New Drug Quality Assessment through Don Henry (301) 796-3878

DATE  
December 15, 2008

IND NO.

NDA NO.  
22-395

TYPE OF DOCUMENT  
Original NDA (electronic)

DATE OF DOCUMENT  
October 16, 2008

NAME OF DRUG  
Capsaicin patch

PRIORITY CONSIDERATION  
S

CLASSIFICATION OF DRUG  
1

DESIRED COMPLETION DATE  
March 15, 2009

NAME OF FIRM: NeurogesX

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |  |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW                  |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY                      |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS                  |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |  |

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION            | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** Request for review and written comment on product stability and expiration dating. The applicant included a statistical analysis of stability data in Section 3.2.P.8 of NDA 22-395.

SIGNATURE OF REQUESTOR  
{see attached signature page}

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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Ali Al-Hakim

12/15/2008 02:35:07 PM



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/

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

# DSI CONSULT: Request for Clinical Inspections

**Date:** December 22<sup>nd</sup>, 2008

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46  
Name of DSI Primary Reviewer (if known)

**Through:** Neville A Gibbs MD, MPH/Clinical Reviewer/DAARP/HFD-170  
Robert Shibuya, MDClinical Team Leader/DAARP/HFD-170

**From:** Tanya Clayton, Regulatory Health Project Manager/Division/HFD-170

**Subject:** Request for Clinical Site Inspections

## **I. General Information**

Application# : NDA 22-395  
Sponsor : NeurogesX, Inc  
2215 Bridgepointe Parkway,  
Suite 200, San Mateo, CA 94404  
Tel 650-358 3300  
Fax 650- 649-1798

Contact : Susan Rinne, MS, VP, Regulatory Affairs

Drug : Capsaicin 8% patch (Qutenza)  
NME : No  
Standard or Priority: Standard  
Study Population: Neuropathic pain associated with postherpetic neuralgia

PDUFA : August, 2009

## **II. Background Information**

This submission is an 8% Capsaicin dermal patch intended for the prolonged reduction of neuropathic pain associated with postherpetic neuralgia (PHN). The two pivotal studies submitted to support the safety and efficacy of Capsaicin 8% Patch are Studies 116 and 117. These studies are similar in design and consist of randomized, double-blind, controlled, multicenter evaluation of the efficacy, safety and tolerability of NGX-4010 for the treatment of PHN.

The duration of participation in the study was 12 weeks, in addition to 14 or more days for Screening. Subjects received a single 60 minute application with a topical local anesthetic on their painful area(s) prior to placement of patch(es) containing active study drug 640 mcg/cm<sup>2</sup> or control

(low-concentration capsaicin, 3.2 mcg/cm<sup>2</sup>) over the affected areas. After treatment, the patch(es) were removed and the treatment area(s) were cleansed with a Sponsor-supplied cleansing gel. Subjects were monitored for at least 2 hours following treatment before being discharged and were asked to return for Follow-Up Visits at 4, 8, and 12 (Termination Visit) weeks after treatment.

Efficacy was assessed daily throughout the study using Numeric Pain Rating Scale (NPRS) scores and by periodic assessments of the modified Brief Pain Inventory (BPI) Short Form, Short-Form McGill Pain Questionnaire (SF-MPQ), Short Form-36 version 2® Health Survey (SF-36v2), Patient Global Impression of Change (PGIC), and Self-Assessment of Treatment (SAT).

Safety and tolerability were assessed by continuous monitoring of adverse events (AEs) and periodic assessments of clinical laboratory parameters, vital signs, physical examinations, electrocardiograms (ECGs), dermal assessments, targeted neurological/sensory assessments, and rescue medication and concomitant medication usage.

### **III. Protocol/Site Identification**

*Include the Protocol Title/# for all protocols to be audited. Complete the following table.*

<b>Site # (Name, Address, Phone number, email, fax#)</b>	<b>Protocol #</b>	<b>Number of Subjects</b>	<b>Indication</b>
<p><b><u>Site # 9</u></b></p> <p><b>Dr. Cynthia Bell</b>  <span style="background-color: #cccccc; display: inline-block; width: 150px; height: 1em; vertical-align: middle;">(b) (4)</span>                      Anchor Research Center,                      680 Goodlette Road North,                      Naples, Florida 34102                      (239)262-4556</p>	<p><u>Study # 116</u>                      A Randomized,                      Double-Blind,                      Controlled Study                      of NGX-4010 for                      the Treatment of                      Postherpetic                      Neuralgia (PHN)</p>	20	The prolonged reduction of neuropathic pain associated with postherpetic neuralgia
<p><b><u>Site # 73</u></b></p> <p><b>L Michael Minehart M.D.</b>                      931 Buena Vista Street, Suite 303.                      Duarte, CA 91010                      Tel(626)-932-3499                      Fax (626)-932-3469                      e-mail&lt;api3030earthlink.net&gt;</p>	<p><u>Study # 116</u>                      A Randomized,                      Double-Blind,                      Controlled Study                      of NGX-4010 for                      the Treatment of                      Postherpetic                      Neuralgia (PHN)</p>	25	The prolonged reduction of neuropathic pain associated with postherpetic neuralgia

Site # (Name, Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
<p><b><u>Site # 129</u></b>   <b>Edwin D Dunteman, MD, M.S.</b>                      A&amp;A Pain Institute of St Louis                      456 N. New Ballas,                      Suite # 154                      St. Louis, MO 63141                      Work Phone: (314) 692-7246                      Fax: (314) 692-8716                      Email &lt;edunteman@aapain.net&gt;</p>	<p><u>Study # 117</u>                      A Randomized,                      Double-Blind,                      Controlled Study                      of NGX-4010 for                      the Treatment of                      Postherpetic                      Neuralgia (PHN)</p>	<p>23</p>	<p>The prolonged                      reduction of neuropathic                      pain associated with                      postherpetic neuralgia.</p>
<p><b><u>Site # 70</u></b>   <b>Marvin D. Tark, MD</b>                      Drug Studies of America,                      1431 White Circle,                      Suite B,                      Marietta, GA 30066                       e-mail &lt;mtark@drugstudies.net&gt;</p>	<p><u>Study # 117</u>                      A Randomized,                      Double-Blind,                      Controlled Study                      of NGX-4010 for                      the Treatment of                      Postherpetic                      Neuralgia (PHN)</p>	<p>15</p>	<p>The prolonged                      reduction of neuropathic                      pain associated with                      postherpetic neuralgia</p>

**IV. Site Selection/Rationale**

The above sites are requested primarily based on the largest proportion of study participants, and the highest between-group difference in change in average pain.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): the highest between-group difference in change in average pain.

Concurrence: (as needed)

\_\_\_\_\_ Medical Team Leader  
 \_\_\_\_\_ Medical Reviewer

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

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Neville Gibbs  
1/2/2009 09:37:34 AM

Robert Shibuya  
1/5/2009 09:15:00 AM

**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/2353fnl.pdf>) YES  NO

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

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

Additional comments:

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

Additional comments:

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



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

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

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/s/

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TANYA D CLAYTON  
11/16/2009



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](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

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

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