

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202278Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 202-278	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Zelrix/Zecuity Established/Proper Name: sumatriptan Dosage Form: iontophoretic transdermal system (patch) Strengths: 6.5mg/4hr		
Applicant: NuPathe Inc.		
Date of Receipt: Original 10/29/10, Resubmission 7/17/12		
PDUFA Goal Dates: 8/29/11 (1 st cycle) and 1/17/13 (2 nd cycle)		Action Goal Date (if different): 1/17/13
Proposed Indication(s): Acute treatment of migraine, with or without aura, in adults		

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)
NDA 20-080 Imitrex Injection	Efficacy
NDA 20-132 Imitrex Tablets	Efficacy

*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)

Applicant bridged to relied-upon product with pharmacokinetic studies and a clinical efficacy study.

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)
Imitrex Injection	20-080	N
Imitrex Tablets	20-132	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").

This application provides for a change in dosage form, from injection/tablet/nasal spray to transdermal patch

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, ^{(b) (4)} 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 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, ^{(b) (4)} 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

Also, there are generic tablets and subcutaneous injection products that are pharmaceutical alternatives.

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):

The applicants lists the above patent numbers, but does not specify to which application(s) these patents apply

- 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): 4816470 and 5037845

Expiry date(s): Expired

- 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

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

/s/

LANA Y CHEN
04/17/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
Revised Label and Labeling Memo**

Date: January 17, 2013
Reviewer: Julie Neshiewat, PharmD
Division of Medication Error Prevention and Analysis
Team Leader: Jamie Wilkins Parker, PharmD
Division of Medication Error Prevention and Analysis
Drug Name and Strength: Zecuity (Sumatriptan) Iontophoretic Transdermal System
6.5 mg / 4 hours
Application Type/Number: NDA 202278
Applicant/sponsor: NuPathe
OSE RCM #: 2012-1597

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised transdermal system label, container (drug-device co-package) labeling, and carton labeling for Zecuity (Sumatriptan Iontophoretic Transdermal System) received on January 17, 2013 (Appendix A). The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the label and labeling for Zecuity and provided comments to the Applicant in OSE Review # 2012-1597, dated November 27, 2012 and January 9, 2013, and comments sent via e-mail on January 16, 2013 and January 17, 2013.

2 MATERIAL REVIEWED

DMEPA reviewed the revised transdermal system label, container (drug-device co-package) labeling, and carton labeling received on January 17, 2013. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2012-1597 dated November 27, 2012 and January 9, 2013, and recommendations sent via e-mail on January 16, 2013 and January 17, 2013 to assess whether the revisions adequately addressed our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised labels and labeling adequately address our concerns from a medication error perspective. DMEPA concludes that the revised transdermal system label, container (drug-device co-package) labeling, and carton labeling are acceptable.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JULIE V NESHIEWAT
01/17/2013

JAMIE C WILKINS PARKER
01/17/2013



Food and Drug Administration
Center for Devices & Radiological Health
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

CDRH/ODE Consult Review ADDENDUM
NDA 202278

Date: January 16, 2013
To: FILE- CDER and OCP
From: Katherine Kim, Biomedical Engineer – DNPMD/PNDB
Subject: Consult review of NuPathe, Inc. (sponsor) NDA submission for the NP101 Migraine Patch; Sumatriptan Iontophoretic Transdermal Patch (device/drug combination)

Addendum Review:

This memo is an addendum to the CDRH/ODE Consult Review Memo, dated December 3, 2012. The sponsor responded to the 10 deficiencies in the 12/3/12 review memo. Please note Brian Pullin, Acting Senior Reviewer in CDRH/ODE/DNPMD/PNDB, reviewed the sponsor’s response to Deficiencies 1-5 to be adequate. Meanwhile, Caroline Strasinger, Chemist in CDER/OPS/ONDQA/DNDQAI/BRIV, reviewed the sponsor’s response to Deficiency 6 to be adequate. Please refer to the email correspondence attached between Dr. Strasinger and Mr. Pullin on December 23, 2012. Meanwhile, the remaining Deficiencies 7-10 are labeling recommendations to CDER, since CDER is the lead center for this submission. CDER requested further input from CDRH regarding the sponsor’s proposed labeling change to delete the contraindication “electrically sensitive support systems.” Feedback from CDRH initially through an email correspondence on January 4, 2013 requested the sponsor to discuss methods of mitigating the potential use of the device in areas near or over electrically-activated implantable or body-woven medical devices (e.g. implantable cardiac pacemaker, body-worn insulin pump, implantable deep brain stimulator). During an internal meeting with CDER on January 9, 2013, there was a consensus that a warning statement against the use of the device in areas near or over electrically-activated implantable or body-woven medical devices is sufficient.

Recommendation:

The deficiencies above regarding the device component of this submission were resolved and there are no remaining issues. Therefore, I recommend that the Zecuity TDS be approved for marketing.

Table with 2 columns and 2 rows. Header: Digital Signature Concurrence Table. Row 1: Reviewer Sign-Off. Row 2: Branch Chief Sign-Off.

From: [Strasinger, Caroline](#)
To: [Pullin, Brian](#)
Cc: [Heimann, Martha R](#); [Kim, Katherine](#)
Subject: RE: Zecuity 202-278
Date: Sunday, December 23, 2012 8:40:50 AM

Thank you Brian for your work this weekend. No further review is necessary. I checked Appendix 2 and the Applicant is very thorough (711 pages) in describing their test protocol and all the items you describe below appear in their outline.

Thank you Brian and Katherine once again and Happy Holidays to you as well!

Caroline

From: Pullin, Brian
Sent: Saturday, December 22, 2012 10:10 PM
To: Strasinger, Caroline
Cc: Heimann, Martha R; Kim, Katherine
Subject: RE: Zecuity 202-278

Dear Caroline,

I should note that I do not have all of the NDA documentation, but I am basing my evaluation on the sponsor's response and Katherine's review memo. I agree that the sponsors responses to questions 1-5 appear acceptable.

The sponsor's response to question 6 references Appendix 2, which I did not receive. Therefore, I cannot evaluate that response. If you cannot wait for a review from CDRH, the sponsor should have provided a complete verification and validation of their latest software update. In short, this should outline the testing done to verify that the software meets the design requirements and the user requirements, including the software integrated into the final device. This should include someone actually attempting to perform many different tasks with the device. The important thing to check is that the sponsor has outlined their protocols and the device has passed all tests (or any failures are logged and are not significant). This ensures that the changes have not introduced new "bugs" into the software. The specifics of each test protocol are not as important as the fact that the sponsor has used a systematic process.

Happy Holidays!
Brian

From: Strasinger, Caroline
Sent: Tuesday, December 18, 2012 9:10 AM
To: Pullin, Brian
Cc: Heimann, Martha R
Subject: Zecuity 202-278

Hello,

The Applicant has responded to Katherine's requests for the iontophoretic device she is reviewing. I looked over them and it appears they have addressed all of the items (Katherine's are #1-6). Because CDER requires no open items at the end of review for a drug product, I will need an addendum stating

the Applicant has sufficiently answered all of the items. I know Katherine is out until after the first of the year so is it possible for you to briefly look at the Applicant's responses and assure that I am correct that they have addressed her concerns adequately? I can write the addendum on her behalf unless you prefer to do it, but I just wanted to be certain that there are no non-approval issues with the device before doing so. I will need to finalize my review by December 24th.

Thank you,

Attached is the response (Only need to look at Items 1-6), Katherine's primary review for reference, and the Applicant referenced Appendix 1. If you need any other attachments that are referenced by the Applicant let me know and I will send them individually (some are pretty large).

<< File: Response_0042_Dec 14.pdf >> << File: NDA 202278 - Review Memo.pdf >> << File: Appendix 1 Q5 Appendix 3 Q8 SOPs 14Dec2012.pdf >>

Caroline Strasinger , PhD

FDA - Office of New Drug Quality Assessment

10903 New Hampshire Ave.

Silver Spring, MD 20993-0002

Ph: 301-796-3776

From: [Kim, Katherine](#)
To: [Chen, Lana Y](#)
Cc: [Pullin, Brian](#)
Subject: RE: NDA 202278: FDA-Proposed PI and NuPathe response-- seeking CDRH input
Date: Friday, January 04, 2013 2:29:39 PM
Attachments: [NDA 202278 Zecuity PI PPI Sponsor Proposed OCT 17 2012.doc](#)

Hi Lana,

Attached are the recommended labeling changes from CDRH/ODE that were uploaded in eroom. I believe the addition of a contraindication [REDACTED] (b) (4) [REDACTED] was reworded by CDER to [REDACTED] (b) (4)

Should the sponsor propose deleting this contraindication, the sponsor should discuss methods of mitigating the potential use of the device in areas near or over electrically-active implantable or body-woven medical devices (e.g. implantable cardiac pacemaker, body-worn insulin pump, implantable deep brain stimulator).

Please note this was discussed with Donald "Skip" Witters (CDRH/OSEL), who is an electromagnetic-compatibility expert, and the above was per his recommendation.

-Katherine

From: Chen, Lana Y
Sent: Wednesday, January 02, 2013 2:55 PM
To: Weisberg, Elijah; Kim, Katherine
Cc: Bouie, Teshara; Strasinger, Caroline; Chen, Lana Y; Bastings, Eric; Kozauer, Nicholas
Subject: FW: NDA 202278: FDA-Proposed PI and NuPathe response-- seeking CDRH input

[Hi Katherine and Elijah,](#)

Please see our request below, from Eric. Attached is the Sponsor's proposed PI fyi.

[thanks,](#)
[Lana](#)

From: Bastings, Eric
Sent: Wednesday, January 02, 2013 2:18 PM
To: Chen, Lana Y
Subject: RE: NDA 202278: FDA-Proposed PI and NuPathe response-- internal goal date?

Lana,

Please ask CDRH to review the sponsor proposed labeling change deleting the statement [REDACTED] (b) (4) [REDACTED] from contraindications. The sponsor's argument is that "As summarized in the Hazard Analysis Summary Report (REP-DHF-NP101-327), ZECUITY TDS is not susceptible to electromagnetic interference per IEC 60601-1-2 and [REDACTED] (b) (4) Report

90914-9 submitted previously. In addition, the device in ZECUITY does not produce sufficient electro-magnetic interference to interfere with other devices. Consequently, NuPathe has omitted the bullet point, (b) (4) in the Contraindications Section (line 65 in FDA proposed PI).”

Thanks.

Eric

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

/s/

LANA Y CHEN
01/17/2013
Placed in DARRTS for CDRH

**PMR/PMC Development Template for Zecuity
PMR # 2000-1**

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Adolescent Pharmacokinetic Study

PMR/PMC Schedule Milestones: Final protocol Submission Date: March 2013
Study/Clinical trial Completion Date: May 2014
Final Report Submission Date: July 2014
Other: _____ MM/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Deferred pediatric study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Deferred pediatric study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Open label, single dose pharmacokinetic study of Zecuity (sumatriptan) iontophoretic transdermal system in adolescents 12 to 17 years of age with a history of acute migraines, which compares the results with appropriate adult historical control data. The number of adolescent migraine patients in this study must be sufficient to adequately characterize the single dose pharmacokinetics of adolescents compared to adults. There must be similar number of patients in the 12 to 14 and 15 to 17 age groups. There must be a reasonable distribution of both sexes in this age bracket.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

**PMR/PMC Development Template for Zecuity
PMR # 2000-2**

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Adolescent Efficacy Study

PMR/PMC Schedule Milestones: Final protocol Submission Date: August 2014
Study/Clinical trial Completion Date: September 2015
Final Report Submission Date: December 2015
Other: _____ MM/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Deferred pediatric study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Deferred pediatric study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized, double-blind, placebo-controlled, parallel group study to evaluate the effectiveness and safety of a single Zecuity (sumatriptan) iontophoretic transdermal system compared to a single placebo iontophoretic transdermal system in adolescents 12 to 17 years of age with a history of acute migraines. An enrichment design for the efficacy study must be used to reduce the placebo effect. The primary efficacy endpoint must be pain freedom at 2 hours. The study must be powered to detect an effect size similar to that seen in the adult population. There must be similar number of patients in the 12 to 14 and 15 to 17 age groups. The protocol must allow the use of appropriate rescue medication after suitable post-dosing interval.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Safety and Efficacy pediatric study
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

**PMR/PMC Development Template for Zecuity
PMR # 2000-3**

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Adolescent Long-Term Safety Study

PMR/PMC Schedule Milestones: Final protocol Submission Date: August 2014
Study/Clinical trial Completion Date: September 2016
Final Report Submission Date: December 2016
Other: _____ MM/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Deferred pediatric study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Deferred pediatric study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Open label, 12-month study to evaluate the long-term safety of Zecuity in adolescents 12 to 17 years of age with a history of acute migraines. Safety assessments must include adverse events, subject and investigator skin irritation evaluations and monitoring of vital signs. The study must evaluate a sufficient number of adolescent migraine patients to be able to characterize the long-term safety of Zecuity when used to treat multiple migraine attacks over one year. Each patient must treat, on average, 1 or more headaches per month for six to twelve months. At a minimum, 200 patients, using an effective dose, must be exposed for six months, and 75 patients, using an effective dose, must be exposed for one year. There must be similar number of patients in the 12 to 14 and 15 to 17 age groups.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

**PMR/PMC Development Template for Zecuity TDS™ (Sumatriptan Succinate)
PMR #2000-4**

PMR Description: Studies to characterize the transdermal absorption of sumatriptan succinate in an *in vivo* mouse skin painting model, using various penetration enhancers.

PMR Schedule Milestones:	Final protocol Submission Date:	<u>April 2013</u>
	Study Completion Date:	<u>September 2013</u>
	Final Report Submission Date:	<u>November 2013</u>
	Other: <u>N/A</u>	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical data for Zecuity TDS, a transdermal iontophoretic system for delivery of sumatriptan succinate, warrant approval at this time; however, the carcinogenic potential of sumatriptan following repeated transdermal administration has not been assessed. An *in vivo* mouse skin painting study is needed to assess the feasibility of conducting a dermal carcinogenicity study of sumatriptan.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

An assessment of carcinogenic potential is required to identify an unexpected, serious risk of adverse effects of sumatriptan, administered by transdermal application, in accordance with ICH and FDA/CDER guidance. The sponsor did not conduct such an assessment or provide data to demonstrate that such an assessment is not feasible.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An *in vivo* repeat-dose dermal painting study (with toxicokinetic [TK] analysis) of sumatriptan succinate conducted in an appropriate mouse model, and using various penetration enhancers.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

**PMR/PMC Development Template for Zecuity TDS™ (Sumatriptan Succinate)
PMR #2000-5**

PMR Description: A dermal (painting) carcinogenicity study of sumatriptan succinate in mice.

PMR Schedule Milestones:	Final protocol Submission Date:	<u>April 2014</u>
	Study Completion Date:	<u>June 2016</u>
	Final Report Submission Date:	<u>December 2016</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical data for Zecuity TDS, a transdermal iontophoretic system for delivery of sumatriptan succinate, warrant approval at this time; however, the carcinogenic potential of sumatriptan following repeated transdermal administration has not been assessed, nor has the sponsor provided sufficient data to document that a dermal carcinogenicity study in mouse is not feasible.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

An assessment of carcinogenic potential is required to identify an unexpected, serious risk of adverse effects of sumatriptan, administered by transdermal application, in accordance with ICH and FDA/CDER guidance. The sponsor did not conduct such an assessment or provide data to demonstrate that such an assessment is not feasible.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A dermal (painting) carcinogenicity study of sumatriptan succinate in mice.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

SALLY U YASUDA
01/15/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	ZECUITY (sumatriptan iontophoretic transdermal system)
Applicant	NuPathe, Inc.
Application/Supplement Number	NDA 202278
Type of Application	Original
Indication(s)	Acute treatment of migraine with or without aura in adults
Established Pharmacologic Class ¹	Serotonin (5HT) 1b/1d receptor agonist (triptan)
Office/Division	ODEI/DNP
Division Project Manager	Lana Chen
Date FDA Received Application	July 17, 2012
Goal Date	January 17, 2013
Date PI Received by SEALD	January 11, 2013
SEALD Review Date	January 14, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*

Selected Requirements of Prescribing Information

• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

NO

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: Please replace <<Insert four-digit year>> with "2013".

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

Selected Requirements of Prescribing Information

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- NO** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment: *The FPI lists Allergic Contact Dermatitis; this is missing from HL.*

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Selected Requirements of Prescribing Information

Comment:

Adverse Reactions

- NO** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *The actual phone number for the manufacturer is missing.*

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *The current date is listed as: "xx/201x"; this should read: 01/2013*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Selected Requirements of Prescribing Information

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)

Selected Requirements of Prescribing Information

12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: The FDA-approved patient labeling must appear at the end of the PI upon approval.

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment: The cross-reference listed under 8.5 is “see Warnings and Precautions (5.1)” and it should reference (5.3).

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

APPEARS THIS WAY ON ORIGINAL

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/s/

ELIZABETH A DONOHOE
01/14/2013

LAURIE B BURKE
01/14/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion**

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: January 10, 2013

To: Lana Y Chen, R.Ph., CAPT-USPHS
Senior Regulatory Project Manager
Division of Neurology Products (DNP)

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)
Division of Consumer Drug Promotion (DCDP)

Subject: NDA 202278
DCDP Comments for draft PPI and IFU for Zecuity (sumatriptan succinate) Iontophoretic Transdermal System

DCDP has reviewed the proposed PPI and IFU for Zecuity (sumatriptan succinate) Iontophoretic Transdermal System. We have reviewed DMPP's comments from 01/08/13 and agree with those changes and have no additional comments at this time.

Thank you for the opportunity to comment on the proposed PPI and IFU.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
01/10/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
Revised Label and Labeling Memo**

Date: January 9, 2013

Reviewer: Julie Neshiewat, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS, Team Leader
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Zecuity (Sumatriptan) Iontophoretic Transdermal System
6.5 mg / 4 hours

Application Type/Number: NDA 202278

Applicant/sponsor: NuPathe

OSE RCM #: 2012-1597

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised transdermal system label, container (drug-device co-package) labeling, and carton labeling for Zecuity (Sumatriptan Iontophoretic Transdermal System) received on December 13, 2012 (Appendix A). The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the label and labeling for Zecuity and provided comments to the Applicant in OSE Review # 2012-1597, dated November 27, 2012.

2 MATERIAL REVIEWED

DMEPA reviewed the revised transdermal system label, container (drug-device co-package) labeling, and carton labeling received on December 13, 2012. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2012-1597 dated November 27, 2012 to assess whether the revisions adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised labels and labeling determined that not all of our previous recommendations were implemented by the Applicant. The Applicant noted that certain statements were kept in capital letters since these statements were short strings of words and would not decrease readability or legibility of the information. The Applicant also relocated the graphic appearing to left of the proprietary name to above the proprietary instead of removing the graphic as requested. We determined that the Applicant's rationale for not implementing these changes is acceptable. However, we identified additional changes that should be made to ensure that the proprietary name, established name, and statement of strength are the most prominent information on the labels and labeling. DMEPA recommends the following recommendations be implemented prior to approval of this application:

A. Container (drug-device co-package) Labeling and Carton Labeling

1. The established name appears to be at least half the size of the proprietary name, but the established name's thin font lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. Relocate the statement of strength to underneath the established name for customary placement. Increase the font size of the statement of strength for more prominence. In order to accommodate these changes, consider removing or minimizing the graphic located above the proprietary name.

B. Carton Labeling

1. As currently presented, the statement "For Transdermal Use Only" is less prominent than the NuPathe logo. Increase the prominence of the statement and place beneath the statement of strength for customary placement.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

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/s/

JULIE V NESHIEWAT
01/09/2013

IRENE Z CHAN
01/09/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: January 8, 2013

To: Eric Bastings, MD
Deputy Director
Division of Neurology Products (DNP)

Lana Y Chen, R.Ph., CAPT-USPHS
Senior Regulatory Project Manager
DNP

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)
Division of Professional Drug Promotion (DPDP)

Subject: OPDP Comments on the draft Prescribing Information (PI) and carton/container label for ZECUITY™ (sumatriptan iontophoretic transdermal system)

This consult is in response to DNP's request for OPDP's review of the proposed labeling for ZECUITY™ (sumatriptan iontophoretic transdermal system).

We appreciate the opportunity to provide comments on the PI. Please see attached PI with our comments incorporated therein.

In addition, we have no comments on the carton/container labeling.

If you have any questions, please contact Quynh-Van Tran, (301) 796-0185, or quynh-van.tran@fda.hhs.gov.

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/s/

QUYNH-VAN TRAN
01/08/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: **January 08, 2013**

To: **Russell Katz, M.D., Director
Division of Neurology Products (DNP)**

Through: **LaShawn Griffiths, RN, MSHS-PH, BSN
Associate Director, Patient Labeling Team
Division of Medical Policy Programs (DMPP)**
**Melissa Hulett RN, BSN, MSBA
Team Leader, Patient Labeling Team
Division of Medical Policy Programs**

From: **Twanda Scales, RN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs**

Subject: **DMPP Review of Patient Labeling (Patient Package Insert,
Instructions for Use)**

Drug Name (established name): **ZECUITY (sumatriptan succinate)**

Dosage Form and Route: **Iontophoretic Transdermal System**

Application Type/Number: **NDA 202278**

Applicant: **NuPathe**

1 INTRODUCTION

On October 29, 2010, NuPathe, Inc. (NuPathe) submitted for the Agency's review a New Drug Application (NDA), 202-278, for ZECUITY (sumatriptan iontophoretic transdermal system). ZECUITY (sumatriptan iontophoretic transdermal system) is a disposable, single-use, co-packaged drug/device combination product that utilizes iontophoretic technology to deliver sumatriptan transdermally for the treatment of acute migraine attacks, with or without aura, in adults. On August 29, 2011, NuPathe received a Complete Response letter from the Agency regarding this original application.

On July 16, 2012, NuPathe resubmitted the original NDA 202-278 following the Complete Response letter from August 29, 2011. This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ZECUITY (sumatriptan iontophoretic transdermal system).

2 MATERIAL REVIEWED

- Draft, ZECUITY (sumatriptan iontophoretic transdermal system) PPI and IFU received on July 16, 2012 and revised by the Review Division throughout the review cycle and received by DMPP on December 31, 2012.
- Draft, ZECUITY (sumatriptan iontophoretic transdermal system) Prescribing Information (PI), received July 16, 2012 and revised by the Review Division throughout the current review cycle and received by DMPP on December 31, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU documents using the Verdana font, size 11.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the prescribing information (PI)

- removed unnecessary or redundant information
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI and IFU are appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI or IFU.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
01/08/2013

MELISSA I HULETT
01/08/2013

LASHAWN M GRIFFITHS
01/09/2013

ADDENDUM TO PMA REVIEW MEMORANDUM for OC/OIVD

DATE: December 21, 2012, addendum to previous
November 29, 2012 memo

TO: The Record

THROUGH: Chief, Orthopedic and Physical Medicine Devices
Branch, Division of Enforcement B, Office of
Compliance, CDRH, WO66-36

	<u> </u>	<u> </u>
	initials	date

FROM: Regulatory Operations Officer, Orthopedic and
Physical Medicine Devices Branch, Division of
Enforcement B, Office of Compliance, CDRH WO66-
3659

SUBJECT: **NDA 202278 – Sumatripan Iontophoretic
Transdermal System / Zecurity (Previously Zelrix)
– Device QS Review (Amendment, Located in
Section 0031/1/1.11/1.11.4 Multiple Module
Information/Guide for Complete Response Letter)**

Applicant: **NuPathe, Inc.**

**221 Washington Street
Suite 200
Conshohocken, PA 19428**

DEVICE: **Sumatripan Iontophoretic Transdermal System /
Zecurity (Previously Zelrix)**

**OC/OIVD
RECOMMENDATION:** *Approvable pending inspection*

FIRM CONTACT (US ADDRESS ONLY):
**Michele A. Roy, RN, MS
NuPathe, Inc,
227 Washington Street,
Suite 200
Conshohocken, PA 19428**

Addendum Review to Firm Response to Deficiencies dated December 14, 2012

Previous Deficiencies

1. (FDA Request 7) You provided SOP GN-005, Rev 00, and SOP QS-008, (b) (4)

[Redacted]

2. (FDA Request 8) You provided a response to deficiencies regarding (b) (4)
In the response, you state that (b) (4)

[Redacted]

The firm provided a response summary titled "Response_0042_Dec 14.pdf".

In response to Request 7, NuPathe states that they have updated the (b) (4)
procedure to rev 4 (SOP QS-008.04). The SOP now
includes (b) (4)

[Redacted]

This response appears adequate.

In response to Request 8, regarding the need for the firm to provide a (b) (4)
protocol, the firm has provided a (b) (4)
PROT-CM-NP101-049.00, in Appendix 3 of the response.

The (b) (4) includes:

(b) (4)

The firm uses a slightly different vocabulary to describe validation activities – (b) (4)

For portions of the process that are verifiable with (b) (4)

and if this is recognized by the FDA, despite the statement from the firm.

This response appears adequate, with a question to CDER for final determination of adequacy of the (b) (4).

LCDR Elijah Weisberg

Prepared: **EWeisberg: 12/21/2012**
Reviewed:
Lead Reviewer: **EWeisberg: 12/21/2012**
Co- Reviewer: **N/A**

Final: **FMLast: date**

cc:
WO66-1521 ODE/POS

OC Doc. No.: **CON1216871**
NDA #202278

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/s/

CAROLINE STRASINGER
12/26/2012
Placed in DARRTS for CDRH

MEMORANDUM

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

DATE: December 14, 2012

TO: Russell Katz, M.D., M.S.
Director,
Division of Neurology Products,
Office of Drug Evaluation I

FROM: Jyoti B. Patel, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 202-278, Zecuity™
(sumatriptan iontophoretic transdermal system NP101)
sponsored by NuPathe Inc.

At the request of the Division of Neurology Products, the Division of Bioequivalence and GLP Compliance (DBGLPC), conducted audit of the clinical portion of the bioequivalence studies listed below. **Please note that the request for inspection of the analytical site at [REDACTED] (b) (4) [REDACTED] was cancelled (Attachment 1).**

Study Number: NP101-023
Study Title: "A phase I, single center, open-label, randomized, single-dose, three-way crossover study to compare the pharmacokinetics and bioequivalence of two NP101 (Sumatriptan Iontophoretic Transdermal Patch) treatments with an oral formulation of Imitrex® in healthy volunteers"

Study Number: NP101-026
Study Title: "A phase I, single center, open-label, randomized, single-dose, two-way, crossover study to compare the pharmacokinetics and bioequivalence of two NP101 (sumatriptan iontophoretic transdermal system) patches and validation testing of the NP101 Pad Detection System"

The objectives of the inspected studies were (1) to compare the pharmacokinetics of NP101 (Sumatriptan Iontophoretic Transdermal System) patches used in a Phase 3 study with NP101 patches with minor modifications; (2) to compare the pharmacokinetics of NP101 patches with currently approved oral formulation of Imitrex® in healthy adult volunteers; and (3) to validate the electronic patch pad detection system.

The FDA audit of the clinical portion of the above studies was conducted at PRACS Institute (Principal Investigator: James C. Freeman), St. Charles, MO (November 1-20, 2012) by ORA investigators Kathleen B. Swat and Karen M. Montgomery (Kansas District Office). The audits included a thorough examination of study records, facilities and equipment, and interviews and discussions with the firms' management and staff.

Following inspection of the clinical site, **a Form FDA-483 was issued (Attachment 2)**. Please note that studies from another application (not related to this application and as such, not listed above) were also audited during this inspection, and a single Form FDA 483 was issued for observations pertaining to all the audited studies. The Form FDA-483 observations for studies NP101-023 and NP101-026, Principal Investigator's (PI) written response to the Form FDA-483 (Attachment 3) and OSI's evaluation of the observations follow.

Clinical site: PRACS Institute, St. Charles, MO

- 1. Failure to prepare or maintain adequate and accurate data pertinent to the investigation. Specifically, for studies NP101-023 and NP101-026, the Delegation of Authority Log is not accurate. Changes to the document are not tracked and maintained. The original document is not accessible and can only be recreated through audit trail records, which lack detail and explanation.**

- In Study NP101-023, the delegation of authority log documents the responsibility start date of 11/2/11 for employee DM, which is after he had performed ECG interpretation and physicals for 28 subjects.
- In Study NP101-026, the delegation of authority log documents employees performing specific study responsibilities prior to delegation by the PI. There were several incidences, when specific protocol related tasks like informed consent, patient screening, ECG reading, and physical examination were performed by employees (b) (6)) prior to delegation by the PI.

Response:

The PI explained in the response that for both studies, the employees accepted responsibilities and the PI approved responsibilities prior to performance of the protocol specific tasks. This information was captured in the electronic Delegation of Authority Log. However, all the information was not documented in the paper Delegation of Authority Log; dates of only the latest or updated events were documented. Employees will be trained for proper documentation requirements.

Evaluation:

The Delegation of Authority Log should accurately capture the complete information of delegation of responsibilities, to avoid any confusion. It is evident from electronic records that the employees had adequate training for the protocol specific tasks. The above observation is not likely to impact the quality and integrity of the overall study data.

2. Protocol Training Logs are not accurate. Dates of protocol training and corresponding date/time of electronic signature do not always match due to manual entry date fields which can be manipulated by the user:

- Two (Study NP101-023) and seven (Study NP101-026) employee training records document training completed after participating in the study protocol.
- Ten (Study NP101-023) and five (Study NP101-026) employee training record audit trails have different training dates and signature dates.

Response:

The PI acknowledged that there was a lack of proper documentation related to employee training records and adequate comments were not listed in the audit trail. The electronic Protocol Training Log captured information each time the protocol review/refresher was completed; however, the printed

report only listed the latest date of training. Employees will be retrained on proper documentation procedures, including audit trail.

Evaluation:

There was a lack of documentation, but based on other documentation, the employees had adequate training to perform the protocol-specific tasks prior to study conduct. This observation is unlikely to impact the quality and integrity of the study data.

3. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. Specifically, in study NP101-026, employee (b) (6) obtained informed consent from subjects (b) (6) 002 and (b) (6) 004 on 4/18/2011, but was not authorized by the PI until 4/19/2011.

Response:

The PI acknowledged that a proper procedure for documentation in the Delegation of Authority Log was not followed. Employee (b) (6) accepted responsibilities and signed off on protocol training on 4/18/2011, and the PI approved responsibilities on 4/19/2011.

Evaluation:

The employee had protocol training prior to the conduct of the specific responsibility. This observation is not likely to impact study data or compromise protection of subject safety.

Conclusions:

Following the review of the EIR, Form FDA-483 observations and Principal Investigator's response, this OSI reviewer recommends that the clinical data generated for studies NP101-023 and NP101-026 are acceptable for further agency's review.

Jyoti B. Patel, Ph.D.
DBGLPC, OSI

Final Classifications:

VAI: Clinical site: PRACS Institute, St. Charles, MO (James C. Freeman, M.D.)
FEI: 3009530688

CC:

Page 5 - NDA 202-278, Zecuity™ (sumatriptan iontophoretic transdermal system NP101)

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Haidar/Patel/Cho/Dejernett/CF

OND/ODEI/DNP/Chen, Lana/Bastings, Eric P/Katz, Russell

OTS/OCP/DCP 1/Bewernitz, Michael

HFR-SW350/ Bromley, Gerald (DIB)/Lopicka, Warren (BIMO)

Draft: JBP 12/14/2012

Edit: SC 12/14/2012; SHH 12/14/2012

OSI file #: 6385; O:\BE\EIRCOVER\202278nup.sum.doc

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: 1458728

ATTACHMENTS:

1. Memo for cancellation of analytical site inspection
2. Form FDA 483 observations
3. PI's response to Form FDA 483 observations

ATTACHMENT - 1

MEMORANDUM

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

DATE: December 13, 2012

TO: Russell Katz, M.D.
Director, Division of Neurology Products
OND/ODEI/DNP

FROM: Sam H Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

Through: William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Inspection request for the bioanalytical portions of
Studies NP101-023 and NP101-026, of NDA 202-278

Regarding the request dated October 1st, 2012, for an inspection of the bioanalytical components of Study NP101-023 and Study NP101-026 conducted at [REDACTED] (b) (4), and per the conversation with Michael Bewernitz on December 11, 2012, we recommend not conducting this inspection for the following reasons:

- The bioanalytical study for the prior submission of NDA 202-278 was inspected at [REDACTED] (b) (4), on April 25-29, 2011, with no objectionable conditions identified
- The same assay and validation were performed for the re-submitted study
- This analytical site has been inspected several times over the past few years, with no serious observations
- Limited OSI resources.

Therefore, we will not process your request for this inspection. Inspection of the clinical components of these studies is not impacted by this memo and will be scheduled.

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/s/

SAM H HAIDAR
12/13/2012

WILLIAM H TAYLOR
12/13/2012

ATTACHMENT - 2

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		
<small>DISTRICT ADDRESS AND PHONE NUMBER</small> 8050 Marshall Drive, Suite 205 Lenexa, KS 66214 (913) 495-5100 Fax: (913) 495-5115 Industry Information: www.fda.gov/oc/industry	<small>DATE(S) OF INSPECTION</small> 11/01/2012 - 11/20/2012 <small>FEI NUMBER</small> 3009530688	
<small>NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED</small> TO: James C Freeman, MD, Principal Investigator		
<small>FIRM NAME</small> Freeman, Dr James C	<small>STREET ADDRESS</small> 400 Fountain Lakes Blvd	
<small>CITY, STATE, ZIP CODE, COUNTRY</small> Saint Charles, MO 63301-4349	<small>TYPE ESTABLISHMENT INSPECTED</small> Clinical Investigator	
<p>This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.</p>		
<p>DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:</p> <p>Four protocols were reviewed during this inspection and the following observations pertain to one or more protocols. Protocols are referred to by their identifying numbers (b) (4) NP101-023, and NP101-026.</p> <div style="background-color: #cccccc; height: 100px; width: 100%; margin-top: 10px;"></div> <p>(b) (4)</p> <p>3. Protocol NP101-023, "A Phase I, Single Center, Open-Label, Randomized, Single-Dose, Three-Way Crossover Study to Compare the Pharmacokinetics and Bioequivalence of Two NP101 (Sumatriptan Iontophoretic Transdermal Patch) Treatments with an Oral Formulation of Imitrex in Healthy Volunteers." This study was sponsored by NuPathe Inc and conducted from October 20, 2011 to November 11, 2011.</p> <p>4. Protocol NP101-026, "A Phase I, Single Center, Open-Label, Randomized, Single-Dose, Two-Way, Crossover Study to Compare the Pharmacokinetics and Bioequivalence of Two NP101 (Sumatriptan Iontophoretic Transdermal System) Patches and Validation Testing of the NP101 Pad Detection System." This study was sponsored by NuPathe Inc and conducted from June 20-27, 2011.</p>		
<p>OBSERVATION 1</p> <p>Failure to assure that an IRB was responsible for the initial and continuing review and approval of a clinical study.</p> <p>Specifically,</p> <div style="background-color: #cccccc; height: 100px; width: 100%; margin-top: 10px;"></div> <p>(b) (4)</p>		
<p>SEE REVERSE OF THIS PAGE</p>	<p><small>EMPLOYEE(S) SIGNATURE</small></p> <p style="font-size: 2em; text-align: center;">UNSIGNED COPY</p>	<p><small>DATE ISSUED</small></p>
<p><small>FORM FDA 483 (09/08) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 1 OF 5 PAGES</small></p>		

ATTACHMENT - 2

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		
<small>DISTRICT ADDRESS AND PHONE NUMBER</small> 8050 Marshall Drive, Suite 205 Lenexa, KS 66214 (913) 495-5100 Fax: (913) 495-5115 Industry Information: www.fda.gov/oc/industry	<small>DATE(S) OF INSPECTION</small> 11/01/2012 - 11/20/2012 <small>FEI NUMBER</small> 3009530688	
<small>NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED</small> TO: James C Freeman, MD, Principal Investigator		
<small>FIRM NAME</small> Freeman, Dr James C	<small>STREET ADDRESS</small> 400 Fountain Lakes Blvd	
<small>CITY, STATE, ZIP CODE, COUNTRY</small> Saint Charles, MO 63301-4349	<small>TYPE ESTABLISHMENT INSPECTED</small> Clinical Investigator	
(b) (4)		
OBSERVATION 2 Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study-related tests . Specifically,		
(b) (4)		
OBSERVATION 3 Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically,		
(b) (4)		
SEE REVERSE OF THIS PAGE	<small>EMPLOYEE(S) SIGNATURE</small> <div style="font-size: 2em; font-weight: bold; text-align: center;">UNSIGNED COPY</div>	<small>DATE ISSUED</small>
FORM FDA 483 (09/08)	PREVIOUS EDITION OBSOLETE	INSPECTIONAL OBSERVATIONS
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<p>NP101-023 and NP101-026</p> <p>4. The Delegation of Authority Log is not accurate. Changes to the document are not tracked and maintained. The original document is not accessible and can only be recreated through audit trail records which lack detail and explanation.</p> <ul style="list-style-type: none"> In study NP101-023, the delegation of authority log documents the responsibility start date of 11/2/11 for employee (b) (6) after he had performed ECG interpretation and physicals for 28 subjects. In study NP101-026, the delegation of authority log documents employees performing specific study responsibilities prior to delegation by the Principal Investigator. The following table illustrates the number of times specific protocol related tasks were performed by employees prior to delegation by the Principal Investigator: <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 10px;"> <thead> <tr> <th style="width: 15%;">Employee</th> <th style="width: 25%;">Informed Consent</th> <th style="width: 25%;">Screening</th> <th style="width: 20%;">ECG Reading</th> <th style="width: 15%;">Physical Exam</th> </tr> </thead> <tbody> <tr> <td>(b) (6)</td> <td></td> <td></td> <td>26</td> <td>29</td> </tr> <tr> <td></td> <td>8</td> <td>6</td> <td></td> <td></td> </tr> <tr> <td></td> <td>2</td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td>15</td> <td>2</td> <td></td> <td></td> </tr> <tr> <td></td> <td>3</td> <td>1</td> <td></td> <td></td> </tr> <tr> <td></td> <td>2</td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td>1</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>			Employee	Informed Consent	Screening	ECG Reading	Physical Exam	(b) (6)			26	29		8	6				2					15	2				3	1				2					1			
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(b) (6)			26	29																																						
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<p>5. Protocol training logs are not accurate. Dates of protocol training and corresponding date/time of electronic signatures do not always match due to manual entry date fields which can be manipulated by the user.</p> <p>In study NP101-023,</p> <ul style="list-style-type: none"> Two employee training records document training completed after participating in the study protocol. Ten employee training record audit trails have different training dates and signature dates. <p>In study NP101-026,</p> <ul style="list-style-type: none"> Seven employee training records document training completed after participating in the study protocol. Five employee training record audit trails have different training dates and signature dates. 																																										
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<small>NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED</small> TO: James C Freeman, MD, Principal Investigator		
<small>FIRM NAME</small> Freeman, Dr James C <small>CITY, STATE, ZIP CODE, COUNTRY</small> Saint Charles, MO 63301-4349	<small>STREET ADDRESS</small> 400 Fountain Lakes Blvd <small>TYPE ESTABLISHMENT INSPECTED</small> Clinical Investigator	
<p>OBSERVATION 4</p> <p>Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others.</p> <p>Specifically,</p> <div style="background-color: #cccccc; height: 80px; width: 100%; margin-top: 10px;"></div> <p style="text-align: right; font-size: small;">(b) (4)</p>		
<p>OBSERVATION 5</p> <p>An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.</p> <p>Specifically,</p> <p>1. Principal investigator did not ensure that study personnel performed only their designated responsibilities as required by the protocol.</p> <div style="background-color: #cccccc; height: 150px; width: 100%; margin-top: 10px;"></div> <p style="text-align: right; font-size: small;">(b) (4)</p> <p>In study NP101-026</p> <ul style="list-style-type: none"> • Employee (b) (6) obtained informed consent from subjects (b) (6)002 and (b) (6)004 on 4/18/11 and was not authorized by the Principal Investigator until 4/19/11. <p>2. (b) (4)</p> <div style="background-color: #cccccc; height: 40px; width: 100%; margin-top: 10px;"></div> <p style="text-align: right; font-size: small;">(b) (4)</p>		
<p>SEE REVERSE OF THIS PAGE</p>	<small>EMPLOYEE(S) SIGNATURE</small> <div style="font-size: 2em; font-weight: bold; text-align: center; padding: 10px 0;">UNSIGNED COPY</div>	<small>DATE ISSUED</small>
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<small>FIRM NAME</small> Freeman, Dr James C	<small>STREET ADDRESS</small> 400 Fountain Lakes Blvd	
<small>CITY, STATE, ZIP CODE, COUNTRY</small> Saint Charles, MO 63301-4349	<small>TYPE ESTABLISHMENT INSPECTED</small> Clinical Investigator	
<div style="background-color: #cccccc; width: 100%; height: 100%;"></div> (b) (4), (b) (6)		
OBSERVATION 6		
<div style="background-color: #cccccc; width: 100%; height: 100%;"></div> (b) (4)		
Specifically,		
<div style="background-color: #cccccc; width: 100%; height: 100%;"></div> (b) (4)		
<div style="background-color: #cccccc; width: 30%; margin: auto; padding: 5px;"> APPEARS THIS WAY ON ORIGINAL </div>		
SEE REVERSE OF THIS PAGE	<small>EMPLOYEE(S) SIGNATURE</small> <div style="font-size: 2em; font-weight: bold; text-align: center;">UNSIGNED COPY</div>	<small>DATE ISSUED</small>
FORM FDA 483 (09/08)	PREVIOUS EDITION OBSOLETE	INSPECTIONAL OBSERVATIONS
		PAGE 5 OF 5 PAGES

ATTACHMENT - 3

December 11, 2012

John Thorsky, District Director
Kansas City District, Food and Drug Administration (FDA).
8050 Marshall Drive, Suite 205
Lenexa, KS 66214

RECEIVED
DEC 12 2012

BY: _____

RECEIVED
CMS # 65001
DEC 12 2012
FEI 3009530688
HFR-SW340

RE: Form FDA 483 Response – FEI Number 3009530688, James C. Freeman, MD – Principal Investigator – Study Protocol(s) (b) (4), NP101-023 and NP101-026 – Inspection Dates: November 01-20, 2012

Dear Mr. Thorsky:

Please find my written response regarding the Form FDA 483 observations that were issued to me at the conclusion of the FDA Inspection on November 20, 2012. The inspection was performed by Investigators Kathleen B. Swat, St. Louis Office, and Karen M. Montgomery, Kansas City District, of the Food and Drug Administration (FDA).

Observation 1:

(b) (4)



ATTACHMENT - 3

Observation 2:

(b) (4)



(b) (4)



Observation 3:

Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.
Specifically,



NP101-023 and NP101-026

4. The Delegation of Authority Log is not accurate. Changes to the document are not tracked and maintained. The original document is not accessible and can only be recreated through audit trail records which lack detail and explanation.

- **In study NP101-023**, the delegation of authority log documents the responsibility start date of 11/2/11 for employee (b) (6) after he had performed ECG interpretation and physicals for 28 subjects.
- **In study NP101-026**, the delegation of authority log documents employees performing specific study responsibilities prior to delegation by the Principal Investigator. The following table illustrates the number of times specific protocol related tasks were performed by employees prior to delegation by the Principal Investigator:

Employee	Informed Consent	Screening	ECG Reading	Physical exam
(b) (6)			26	29
(b) (6)	8	6		
(b) (6)	2			
(b) (6)	15	2		
(b) (6)	3	1		
(b) (6)	2			
(b) (6)	1			

ATTACHMENT - 3

5. Protocol training logs are not accurate. Dates of protocol training and corresponding date/time of electronic signatures do not always match due to manual entry date fields which can be manipulated by the user.

In study NP101-023,

- Two employee training records document training completed after participating in the study protocol.
- Ten employee training record audit trails have different training dates and signature dates.

In study NP101-026,

- Seven employee training records document training completed after participating in the study protocol.
- Five employee training record audit trails have different training dates and signature dates.

Observation 3 Response:

1. *The system used to document dosing is a proprietary system to the investigative site. It identifies the general location the patch is to be placed and the randomization of that patch. The investigator site's standard operating procedure outlining this process was to document the application and dose information of the study product(s). I, as Principal Investigator, have instructed the investigator site to update this practice. The documentation now requires the identification of the product(s) placed, in addition to the application and dose. Training on the updated procedure was completed on 03DEC2012.*
2. *The staff did not view the papers used for mounting the collected used patches as source documentation. When the patches were removed from the subjects, they were placed on a piece of paper and the subject number was recorded to determine which patch was administered. These documents were retained for a period of time to allow for an investigation. Following the completion of the investigation, the patches were disposed of per Section 12.3 of the protocol. It is acknowledged the pages documenting the subjects who were misdosed should have been maintained. In January of 2013, the investigative site has committed to providing staff with a refresher of Good Documentation Practices training in concert with their existing SOP. In addition, the training will encompass how to conduct proper investigations and what documentation must be maintained following the completion of the investigation.*
3. *The incident was reported to the investigator site's Help Desk on January 4, 2011 and a subsequent investigation showed no loss of data or missing time points during the period of time in question. The deviations were reported to the Sponsor, but at the time of these trials, these types of deviations were not reported to the IRB per verbal request of the IRB Chairman. I, as Principal Investigator, was also not notified which would have allowed for the assessment of impact to the subjects or data. However, because the subjects were to receive equivalent doses, it posed no safety risk to those subjects. In 2011, the investigative site implemented an incident reporting system in which any protocol deviation would be documented and reviewed by staff. These deviations are to be included in reports to the Sponsor and IRB. The investigator site does have back-up paper documentation in case of any problems*

ATTACHMENT - 3

with the computer system. Staff will be retrained on how to determine when they should implement the transition from electronic source documentation to paper source documentation should there be a system delay.. This training will occur before January 15, 2013

4. The electronic Delegation of Authority Log does maintain full electronic audit trails that are compliant with 21CFR Part 11. The date placed on the Delegation Log (Responsibility Start Date) is determined by the latest of the following events: Protocol Review, Employee Acceptance of Responsibilities, and Principal Investigator Approval of Responsibilities.
- In study NP101-023, Employee (b) (6) accepted responsibilities and the Principal Investigator approved responsibilities on 30SEP2011, protocol training was originally signed off on 30SEP2011 and updated on 02NOV2011.
 - In study NP101-026,
 - a. Employee (b) (6) accepted responsibilities on 19MAR2012, signed off on protocol training originally on 19MAR2012 and completed refresher training on 16JUL2012 and the Principal Investigator approved responsibilities on 18MAR2012.
 - b. Employee (b) (6) accepted responsibilities on 18APR2012, signed off on protocol training originally on 18APR2012 and completed refresher training on 06JUN2012 and the Principal Investigator approved responsibilities on 19APR2012
 - c. Employee (b) (6) and (b) (6) accepted responsibilities and signed off on protocol training on 18APR2012, the Principal Investigator approved responsibilities on 19APR2012.
 - d. Employee (b) (6) accepted responsibilities on 26APR2012, signed off on protocol training originally on 26APR2012 and completed refresher training on 06JUN2012 and the Principal Investigator approved responsibilities on 19APR2012.
 - e. Employee (b) (6) accepted responsibilities on 18APR2012, signed off on protocol training originally on 18APR2012 and completed refresher training on 12JUN2012 and the Principal Investigator approved responsibilities on 19APR2012.
 - f. Employee (b) (6) (incorrectly identified as (b) (6)) accepted responsibilities on 20MAR2012, signed off on protocol training originally on 20MAR2012 and completed refresher training on 06JUN2012 and the Principal Investigator approved responsibilities on 19MAR2012.

Staff, including the Principal Investigator, were not trained appropriately to understand the Delegation of Authority Log documentation requirements of; Protocol Training, Acceptance of Responsibilities and Principal Investigator Approval of Responsibilities. These items must all be completed and signed off prior to performing the delegated study activities. This has been corrected with additional training regarding this documentation to be completed before January 15, 2013. In addition, an upcoming release of the investigator site electronic source program (Q2 2013) will be enhanced to list the sequence of protocol training now captured in the audit trail.

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5. *The electronic Protocol Training Log captures the documentation of each time the protocol review/refreshers is completed, but the printed report only lists the latest date of training. The program was designed to allow for the documentation of past dates in some situations (e.g., computer downtime, inability to access a computer at the time of the protocol review, etc.); however, anytime a date entered is different than the signature date, a comment is required to explain the reason for the late entry. Staff was instructed to update their protocol training within the system for each protocol version, amendment, refresher session, etc. The reason for the additional date should be listed in the audit trail. We acknowledge there was a lack of compliance to the approved procedures not identified internally. The investigator site will re-train staff on the proper documentation procedures, including appropriateness of audit trail comments for protocol training by January 15, 2013. The investigator site will also be updating the design of the protocol review module of the investigator site electronic source program in Q2 2013 to document the review of multiple versions/amendments of a study protocol.*

Observation 4:

[REDACTED] (b) (4)

Specifically,

[REDACTED] (b) (4)

ATTACHMENT - 3

Observation 5:

An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

1. The Principal Investigator did not ensure that study personnel performed only their designated responsibilities as required by protocol.



In study NP101-026

- Employee (b) (6) obtained informed consent from subject (b) (6)002 and (b) (6)004 on 4/18/11 and was not authorized by the Principal Investigator until 4/19/11.

2.



ATTACHMENT - 3

[Redacted]

(b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

Observation 6:

[Redacted]

(b) (4)

Specifically,

[Redacted]

(b) (4)

Observation 6 Response:

(b) (4)

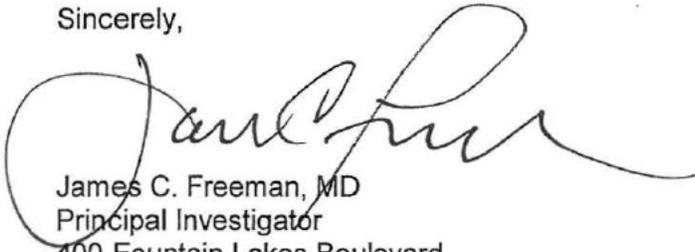
In conclusion, I would like to thank both Ms. Swat and Ms. Montgomery for such a well conducted inspection and for their professionalism and observations during the inspection.

Please include this response in the Agency's inspection file and provide it to anyone who submits a Freedom of Information Act (FOIA) request to the agency.

I, as Principal Investigator, take my role very seriously and will ensure these areas of non-compliance are resolved and all training and corrective action is implemented within the committed timeframe.

Please do not hesitate to contact me should you have any additional questions or require clarification in finalizing the Establishment Inspection Report.

Sincerely,



James C. Freeman, MD
Principal Investigator
400 Fountain Lakes Boulevard
St. Charles, MO 63301

cc:

Ms. Kathleen B. Swat, Investigator, Food and Drug Administration
15 Sunnen Dr.
Suite 113
St. Louis, MO 63143

Ms. Karen M. Montgomery, Investigator, Food and Drug Administration
15 Sunnen Dr.
Suite 113
St. Louis, MO 63143

Dr. Sam H. Haidar, Ph.D.(HFD-45) Chief, Bioequivalence Investigations, Food and Drug Administration-CDER
WO51, Room 5330
10903 New Hampshire
Silver Spring, MD 20993

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/s/

JYOTI B PATEL
12/14/2012

SAM H HAIDAR
12/16/2012

M E M O R A N D U M

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

DATE: December 14, 2012

SUBJECT: Evaluation of Prism Clinical Research response to OAI Untitled Letter issued 8/30/2012

FROM: Charles R. Bonapace, Pharm.D.
Chief (Acting), Good Laboratory Practice (GLP) Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations (OSI)

William H. Taylor, Ph.D.
Director, Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations (OSI)

TO: OSI File BE6173, NDA 202-278

Summary: This memo is a review of the response from Prism Clinical Research, dated September 25, 2012, in response to an OAI Untitled Letter issued on August 30, 2012. A two-item Form FDA 483 was issued at the close-out of the inspection in June 2011 and one of the observations included a failure to retain reserve samples of the test article and the reference standard for the audited bioequivalence study. The firm responded to the Form FDA 483 on July 12, 2011 and OSI found the firm's response and corrective actions inadequate to prevent recurrence of the violation of retention sample requirements. An OAI Untitled Letter was issued on August 30, 2012. Upon the review of firm's September 2012 response to the OAI Untitled Letter, OSI concludes the firm has taken appropriate corrective actions to prevent recurrence of the violation in future studies.

Review and Evaluation:

1. Failure to meet the regulatory requirements for retention of reserve samples for bioavailability or bioequivalence study [21 CFR 320.38 and 320.63].

In the July 12, 2011 response to the Form FDA 483, the firm agreed to implement a new procedure to identify studies that require reserve samples to be retained. As part of the new procedure, the sponsor will be requested to complete paperwork indicating whether

reserve samples are required to be retained for studies contracted by Prism Clinical Research. As noted in the OAI Untitled Letter dated August 30, 2012, 21 CFR 320.38 and 21 CFR 320.63 state that it is the responsibility of the Contract Research Organization (CRO), not of the sponsor, to collect and retain reserve samples. In the response to the OAI Untitled Letter dated September 25, 2012, Prism Clinical Research stated that they implemented further corrective actions consisting of amending existing Standard Operating Procedures, Work Instructions, and Retention of BE/BE Samples Form and creating a new Standard Operating Procedure titled "Retention of Reserve Samples for Bioequivalence and Bioavailability Studies". The corrective actions clarify that Prism Clinical Research is responsible for randomly selecting and retaining the required number of reserve samples for all bioavailability and bioequivalence studies. In addition, the reserve samples will be maintained in the original container and will not be returned to the sponsor following the completion of the study.

Recommendation: The response dated September 25, 2012 further clarifies that Prism Clinical Research is responsible for selecting and retaining reserve samples for bioavailability and bioequivalence studies. Based on our review and evaluation of the response, it appears that the item listed in the OAI Untitled Letter has been adequately addressed and appropriate corrective actions have been taken by Prism Clinical Research to prevent recurrence of the violation in future studies.

cc: DARRTS

CDER OSI PM TRACK

OSI/Moreno

OSI/DBGLPC/Taylor/Haidar (b) (4) Cho/Bonapace/Dejernet/CF

DNP/Katz/Chen

OCP/Men/Parepally

HFR-CE8590/BIMO/Bigham

HFR-CE8590/Investigator/Singh

Draft: CRB 12/11/2012

Edit: SC 12/12/2012

File: 6173

FACTS: 1258517

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB/NDA 202-278_Sumatriptan_Prism Clinical Research/Memo to file

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/s/

CHARLES R BONAPACE
12/14/2012

SAM H HAIDAR
12/14/2012

WILLIAM H TAYLOR
12/14/2012

M E M O R A N D U M

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

DATE: December 13, 2012

TO: Russell Katz, M.D.
Director, Division of Neurology Products
OND/ODEI/DNP

FROM: Sam H Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

Through: William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Inspection request for the bioanalytical portions of
Studies NP101-023 and NP101-026, of NDA 202-278

Regarding the request dated October 1st, 2012, for an inspection of the bioanalytical components of Study NP101-023 and Study NP101-026 conducted at [REDACTED] (b) (4), and per the conversation with Michael Bewernitz on December 11, 2012, we recommend not conducting this inspection for the following reasons:

- The bioanalytical study for the prior submission of NDA 202-278 was inspected at [REDACTED] (b) (4), on April 25-29, 2011, with no objectionable conditions identified
- The same assay and validation were performed for the re-submitted study
- This analytical site has been inspected several times over the past few years, with no serious observations
- Limited OSI resources.

Therefore, we will not process your request for this inspection. Inspection of the clinical components of these studies is not impacted by this memo and will be scheduled.

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

/s/

SAM H HAIDAR
12/13/2012

WILLIAM H TAYLOR
12/13/2012



Food and Drug Administration
Center for Devices & Radiological Health
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

CDRH/ODE Consult Review
NDA 202278

Date: December 3, 2012
To: FILE- CDER and OCP
From: Katherine Kim, Biomedical Engineer – DNPMD/PNDB
Subject: Consult review of NuPathe, Inc. (*sponsor*) NDA submission for the NP101 Migraine Patch; Sumatriptan Iontophoretic Transdermal Patch (*device/drug combination*)

Summary / Recommendation

CDER requested a CDRH consult to review the device component (iontophoresis patch) that was submitted as a combination drug/device product in this NDA. The information provided in this submission is insufficient to demonstrate the device is safe and effective for the proposed intended use. I recommend the sponsor address the deficiencies at the end of this memo in order to proceed with the review of this submission.

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I Submission History

This memo is a review of the sponsor's response to our Discipline Review Letter for Additional Information, dated July 15, 2011. Please note that Geeta Pamidimukkala was the CDRH consult reviewer for the original submission. A summary and discussion of the sponsor's response to our deficiency is provided below.

The following was modified from Ms. Pamidimukkala's review memo dated 7/18/11):

Geeta Pamidimukkala was the CDRH consult reviewer for NuPathe's IND submission (IND 74,877). The purpose of the IND was to perform a clinical study to evaluate the two design proposals for the NP101 Migraine Patch (iontophoretic transdermal patch) for the treatment of migraine headache with or without aura in adults. The FDA review team met with the sponsor on March 4, 2010 for a meeting to discuss the additional information that would likely be required for a subsequent NDA. In the course of the IND review Ms. Pamidimukkala informed the sponsor that a separate 510(k) clearance for the patch is not necessary as both the drug and device will be reviewed in the NDA and NDA approval applies to the device component as well. However, should the sponsor wish to market the device alone, without sumatriptan or any other specified drug/ionic solution, the sponsor should submit the device for review in a separate 510(k). NDA approval applies to the combination of the drug and device and cannot be applied to the device separately. The sponsor subsequently submitted this NDA for the use of the NP101 iontophoresis device (trade name: Zelrix Iontophoretic System) for trans dermal delivery of sumatriptan for treatment of migraine headache in adults.

CDRH/ODE Review of Device components in NDA submission

The majority of the device information is contained in section 3.2.R.4. The sponsor also provided several attachments with additional information regarding device related information. Below is a complete review of all information regarding the device, except manufacturing, provided within NDA 202278.

II Response to Deficiency

43. Provide the battery specification sheet that includes battery capacity for the 2 [REDACTED] (b) (4) batteries.

Sponsor's Response: The battery manufacturer has changed from [REDACTED] (b) (4). NuPathe material specification for these batteries is referenced in Table 6 of Section 3.2.R.4.1. Battery properties are discussed in Section 3.2.R.4.1.3.2.5 and the battery verification report is referenced in Section 3.2.R.4.3.1.1.2.

Reviewer's Comment: The response is acceptable. Please note the sponsor changed the battery manufacturer from [REDACTED] (b) (4).

44. Regarding stability of the clinical and commercially packaged systems after 9 months and 6 months storage, respectively provided to support an expiration date of [REDACTED] (b) (4) months, address the following:
- a. NuPathe Stability Protocol for NP101 Documents for Device Stability, Lot MBR-75-NP101-007-0012 and Lot MBR-75-NP101-017-0001 (Document Numbers: Prot-CM-NP101-007 and Prot-CM-NP101-008, respectively) states the protocol was amended to [REDACTED] (b) (4)

Sponsor's Response: E-Patch testing was amended to reflect continuous improvement in testing and device revisions. In particular, the [REDACTED] (b) (4)

(b) (4)

Additional information on device testing is available in Section 3.2.R.4.4.5.4 and Section 3.2.R.4.3.1.3.

Reviewer's Comment: The response is acceptable. The sponsor states “ (b) (4)

In Section 3.2.R.4.4.5.4, the sponsor states “ (b) (4)

- b. The document “Post-approval Stability Protocol and Stability Commitment.” In Section 3.2.P.8.2 of the original submission states that NuPathe intends to (b) (4)
- Provide a rationale for why these evaluations will not be conducted.

Sponsor's Response: Section 3.2.R.4.3, Table 8 provides the (b) (4) **requirements.**

Reviewer's Comment: The response is acceptable. The sponsor provided the (b) (4) **in Table 8 of Section 3.2.R.4.3, which included** (b) (4)

- c. Provide the pass/fail criteria for the (b) (4).

Sponsor's Response: (b) (4) **is tested during** (b) (4), **with acceptance criteria provided in Section 3.2.R.4.1.2.1.3. In addition,** (b) (4) **, as discussed in Section 3.2.P.5.1. As noted above,** (b) (4)

Acceptance criteria are provided in the relevant component sections of Section 3.2.R.4.1. In addition, (b) (4) **. Acceptance criteria are provided in Section 3.2.P.5.1.**

Reviewer's Comment: The response is acceptable. (b) (4) **Meanwhile, the acceptance criteria for** (b) (4) **are the following:**

Operating Time
(b) (4)

Current Delivery
(b) (4)

These acceptance criteria are consistent with the device specifications in Table 1 of the Device Description Section.

- d. Clarify to what extent the shelf life validation evaluated the potential for corrosion (or other break down) of the power supply.

Sponsor's Response: (b) (4) *and relevant testing, including that related to (b) (4), is discussed in Section 3.2.R.4.3.*

Reviewer's Comment: The response is acceptable. The (b) (4)

45. Regarding biocompatibility, test reports from the completed cytotoxicity, irritation, and dermal sensitization evaluations were provided to demonstrate biocompatibility of patient contacting device components. The test article in each report is described as the "E-Patch (with (b) (4) removed); testing (b) (4), pad transfer ring, overtape with adhesive, foam barrier with adhesive." Confirm that the evaluated test articles are identical to the final device materials intended for commercial distribution. Be advised that biocompatibility should be established for the device you intend to market.

Sponsor's Response: *The referenced test materials ((b) (4) pad transfer ring (b) (4) overtape, or foam) have not changed and are identical to the to be marketed product. To allow for (b) (4) the adhesive used for the pad transfer rings was changed to (b) (4). Biocompatibility test reports are provided in Section 3.2.R.4.4.4.*

Reviewer's Comment: The response is acceptable. The sponsor states "To allow for (b) (4), the adhesive used for the pad transfer rings was changed to (b) (4) Medical Grade Transfer Adhesive. Biocompatibility test reports are provided in Section 3.2.R.4.4.4." During a CDER Internal Review Meeting on December 3, 2012, it was noted that this adhesive for the pad transfer rings was not a patient-contacting device component. Therefore, the sponsor provided adequate biocompatibility testing for all patient-contacting device components identical to the final device materials intended for commercial distribution.

Please note there were reports of several adverse events relating to administration site conditions (e.g., itching, stinging, rash) in three clinical studies (i.e., NP101-024, NP101-025, NP101-026). Refer to CDER review memos for discussion of these adverse events.

46. Regarding Software/Firmware the following modes in the software description section of the submission (section 8.2 of 3.2.R.4) are listed and described: sleep mode, self-test, test mode, active mode, self-test fail mode, (b) (4) mode. There are discrepancies in the naming convention and description of each mode within the software related documents provided in attachments 17-48. Address the following:

- a. The architecture design report (attachment 19) states the device will (b) (4)

(b) (4) mode is not referenced or described anywhere else in the submission. Clarify what is meant by (b) (4) mode.

Sponsor's Response: *Due to modifications in the firmware, a new architecture design report has been provided in Section 3.2.R.4.2. Throughout the verification and validation process NuPathe worked with (b) (4) to standardize the terminology used to describe the firmware modes.*

Reviewer's Comment: The response is acceptable. The sponsor appears to have removed the (b) (4) mode in the architecture design report.

- b. The architecture design report lists a (b) (4) mode. This mode is not referenced or described anywhere else in the submission. Clarify what the (b) (4) mode is, its functions, and to what extent its performance was validated.

Sponsor's Response: *Section 3.2.R.4.2.3.3 includes a description and diagram of the (b) (4)*

Reviewer's Comment: The response is not acceptable. Section 3.2.R.4.2.3.3 describes the (b) (4)

Please refer to the deficiencies.

47. Regarding Software/Firmware address the following issues with the "self-test," "test," "active," and (b) (4) modes:

- a. Clarify if the (b) (4)

Sponsor's Response: *Separation of the Self-Test and Test Mode is discussed in several sections throughout 3.2.R.4 of the NDA. Section 3.2.R.4.1, Table 3 is the first instance to show visualization of the separation of the modes and notes that (b) (4)*

Reviewer's Comment: The response is not acceptable. In Section 3.2.R.4.1, Table 3, the sponsor states that the Self-Test mode verifies (b) (4)

mode examines the (b) (4)

. The status of (b) (4)

In Section 3.2.R.4.2.4.1.3, the sponsor states that (b) (4)

Figure 9 of Section 3.2.R.4.2.4.1.3 states all evaluated parameters in th (b) (4)

Please refer to the deficiencies.

- b. Clarify if the device will enter (b) (4)

Sponsor's Response: *Section 3.2.R.4.2.4.1.4 notes that the device will immediately enter*
(b) (4)

Reviewer's Comment: **The response is acceptable.**

- c. Clarify if there is a (b) (4)

Sponsor's Response: *Section 3.2.R.4.2.4.1.5 discusses the immediate move from*
(b) (4)

Reviewer's Comment: **The response is acceptable.**

- d. Clarify if there is a limit to the number of times a device can be (b) (4)

Sponsor's Response: *The device*
(b) (4)

Additional information is provided in Section 3.2.R.4.2.

Reviewer's Comment: **The response is not acceptable. The sponsor states** (b) (4)
" **In the**
Architecture Design Chart, the device enters (b) (4)
Please refer to the
deficiencies.

- e. Clarify if the device remains in (b) (4)

Sponsor's Response: *This clarification is noted in the discussion of safety features in Section 3.2.R.4.2.3.4.*

Reviewer's Comment: **The response is not acceptable. In Section 3.2.R.4.2.3.4, the**
sponsor states (b) (4)
Please refer to the (4)

deficiencies.

- f. State what is the expected result if the On button is depressed at any point once the device is no longer in Sleep mode.

Sponsor's Response: *As discussed in Section 3.2.R.4.2.3.5, the firmware will acknowledge*

(b) (4).

Reviewer's Comment: The response is acceptable. In Section 3.2.R.4.2.3.5, the sponsor states “

(b) (4)

48. Regarding the Hazard Analysis provided in attachment 17 of the original submission which identified hazards associated with firmware or hardware failure, address the following:

- a. The analysis is incomplete as it did not evaluate potential hazards associated with use of the device in other categories (e.g., electrical, operational, environmental, mechanical). Update the hazard analysis to include all potential hazards that result from device use. Alternatively, provide a rationale for why identification and evaluation of other hazards have been omitted from the analysis.

Sponsor's Response: *Section 3.2.R.4.1.4 describes the Risk Control activities that have taken place throughout design development. NuPathe report REP-DHF-NP101-296 provides the overall product assessment of risk.*

Reviewer's Comment: The response is not acceptable. The sponsor provided a revised hazard analysis in the REP-DHF-NP101-296 report. However, the analysis is incomplete as it did not fully evaluate the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards. Therefore, the sponsor should update the hazard analysis to include a description of all potential hazards (e.g., electrical, operational, environmental, mechanical) presented by this device, the causes and severity of the hazards, the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards. Please refer to the deficiencies.

- b. Burns and blistering have been reported as adverse events for iontophoretic drug delivery patches; however the Hazard Analysis did not identify this hazard. Update the Hazard Analysis to include this risk and all potential causes, along with appropriate mitigating actions.

Sponsor's Response: *The risk assessment and analysis referenced in item 'a' identified the need to protect the patient from misassembly and led to the development and implementation of the Pad Detection System (PDS). This is discussed in detail in Section 3.2.R.4.1.4.3.1. Also refer to Section 2.5.6 and Section 2.5.7 for further discussion on risk benefit.*

Reviewer's Comment: The response is acceptable. The sponsor provided validation testing of the newly implemented Pad Detection System (PDS), which prohibits the E-patch from entering active dosing mode when medication pads were misaligned or absent. In the REP-CL-NP101-026 study, “a total of 140 NP101 patches with the PDS were applied to subjects with the medication pad(s) misaligned or missing. The misaligned and missing pads resulted in the anode and/or cathode electrode of

the patch exposed directly to the skin of the subjects. The PDS functioned correctly for all 140 patches with none of the incorrectly assembled patches turning on (entering active dosing mode)."

- c. The drug and salt imbibed pads have a very similar appearance and it is possible for users to inadvertently switch the pads between the anode and cathode. Address the potential for such an occurrence and discuss the potential hazards to the patient. Update the Hazard Analysis accordingly.

Sponsor's Response: *The co-packaging system (Section 3.2.P.2.4.2) reduces the potential for 'pad switching'. If it occurs, it will be detected by the Pad Detection System (PDS). This is noted in Section 3.2.R.4.2.3.1 in the discussion regarding PDS operation. Stage (b) (4) of the PDS determines that the drug and salt pads are placed on the correct electrode.*

Reviewer's Comment: **The response is acceptable. The sponsor redesigned the device to feature a Pad Detection System (PDS). Stage (b) (4) of this system determines that the pads are in the correct orientation (i.e., the salt pad is on the Cathode) and the salt pad is properly aligned (i.e., all (b) (4) are covered by the pad) (drug pad alignment is determined in Stage (b) (4)).**

- d. The Software Safety Report in attachment 17 states the analysis was performed on software Version (b) (4). Clarify if all risk controls identified in the Hazard List table have been implemented in the software Version (b) (4) (the version that is intended for commercial distribution).

Sponsor's Response: *Software verification and validation was performed on (b) (4), which is the software version of the to be marketed product. Section 3.2.R.4.2.7 details the firmware Verification and Validation and notes that (b) (4) was the version validated.*

Reviewer's Comment: **The response is acceptable.**

49. All validation and verification activities were completed on firmware version (b) (4), however the E-patch will be commercially released with version (b) (4) and a full validation of this version was never completed. A memo in attachment 48 stated that the differences between the two versions are not expected to impact performance and that version (b) (4) passed the (b) (4) test and the (b) (4) test. Provide the test report (method, results, discussion) for these completed tests and provide a rationale for why these two tests alone are sufficient. Alternatively, complete a full validation and verification of the firmware version you intend to use in the commercial product.

Sponsor's Response: *The NP101 firmware is described in detail in Section 3.2.R.4.2 of the NDA. The final version of firmware in the proposed to be marketed product is (b) (4). Verification and validation of this final firmware version is discussed more specifically in Section 3.2.R.4.2.7.*

Reviewer's Comment: **The response is not acceptable. The sponsor indicates that the final version of firmware in the proposed to be marketed product is (b) (4). However, the Verification and Validation documentation of this final firmware version in Section 3.2.R.4.2.7 does not provide a complete description of the validation and verification activities at the unit, integration, and system level. The sponsor should provide unit, integration, and system level test protocol, including pass/fail criteria, test report, summary, and test results. Please refer to the deficiencies.**

50. Section 2 of 3.2.R.4 of the original submission declares conformity to several standards, including IEC 60601-2-2 (2006), and Medical Electrical Equipment Part 2-2: Particular requirements for the safety of high frequency surgical equipment. It is not apparent how this standard is applicable to the device as the device does not generate or deliver high frequency current. Explain the extent to which the device

conforms to this standard.

Sponsor's Response: *The device does not generate or deliver high frequency current. During the March 2010 pre-NDA CMC meeting, FDA recommended conformability testing of the device in accordance with ANSI/AAMI Standard HF18-2001 (Electrosurgical Devices), which has since been superseded by ANSI/AAMI/IEC 60601-2-2:2009 (Medical Electrical Equipment – Part 2-2: Particular requirements for basic safety and essential performance of high frequency surgery equipment and high frequency surgical accessories). Testing for conformability of NP101 was performed and results met the established standard. This is explained in the NDA resubmission in Section 3.2.R.4.4.6.*

Reviewer's Comment: The response is acceptable. The request for the sponsor to provide patch conformability testing to the thigh and arm during a pre-NDA meeting on 3/4/2012 is consistent with Ms. Pamidimukkala's prior review memo. During that meeting, Ms. Pamidimukkala suggested the firm reference ANSI/AAMI HF 18 for guidance in method development. That standard is no longer recognized by the Agency and is superseded by IEC 60601-2-2. Therefore, the sponsor used this standard (IEC 60601-2-2:2009 Section 201.15.101.7) for test method development.

51. Evaluation of patch conformability was conducted according to IEC 60601-2-2 standard. All patches met the acceptance criteria of the standard (less than ^(b)₍₄₎ % lift after 1 hour of placement on the forearm); however, multiple patches showed signs of lift at the edges and near the power supply. Based on this evaluation, it is not clear if the patches will adhere completely for the full 4 hour dosing period. Incomplete adherence of the electrodes could result in injury to the patient. Conduct an evaluation of the conformability of the patch (or extent of patch lift) for the full 4 hour duration of use.

Sponsor's Response: *A Phase 1 study (NP101-024) was conducted in healthy volunteers to perform conformability testing of the NP101 patch to comply with IEC 60601-2-2 requirements. Conformability testing showed that NP101 patches adhered for the 4-hour application time and met the acceptance criteria according to guidance provided by the American National Standards Institute/Association for the Advancement of Medical Instrumentation/International Electrotechnical Commission (ANSI/AAMI/IEC) 60601-2-2:2009. NP101 conformability testing is also discussed in Section 2.7.4.1.3.1, Section 3.2.R.4.1.4.3.2, and Section 3.2.R.4.4.6.*

Reviewer's Comment: The response is acceptable.

52. The current density distribution evaluation was conducted using FEA modeling and determined that the highest degree of non-uniformity occurs at ^(b)₍₄₎ and is less evident at the skin surface when used correctly (i.e., imbibed pads completely cover the electrode areas and entire pad area contacts skin). The 120 day safety update you provided lists several adverse events relating to administration site conditions including 2 instances of moderate burns and 3 instances of severe burns. Burns under electrodes typically occur due to areas of high focused current delivery. Conduct an evaluation of the current density distribution of the device in use for complete and incomplete patch adherence scenarios. Additionally, provide a discussion on scenarios that would result in burns using the device.

Sponsor's Response: *Current density distribution studies are discussed in Section 3.2.R.4.4.5. Scenarios that could result in skin events associated with high current density were addressed during risk assessment. A summary is provided in Section 3.2.R.4.1.4.3.1. The Pad Detection System (PDS) was developed to address the risk of skin events associated with improper use. The PDS is discussed in Section 3.2.R.4.1.3.2.3.*

Reviewer's Comment: The response is acceptable. In Section 3.2.R.4.1.4.3.1, the sponsor states "The functionality of the PDS was evaluated in clinical study NP101-025. In this study, 298 patches with misaligned or missing salt and/or drug pads were applied to subjects. The results of the study demonstrated that the PDS was 100% accurate in recognizing missing or misaligned drug or salt pads and preventing the patch from activating. The PDS was validated in clinical study NP101-026. In this study, a total of 140 NP101 patches were applied to the subjects with the medication pad(s) misaligned or missing. The misalignment and missing pads resulted in the anode and/or cathode of the patch exposed directly to the skin of the subjects. The PDS functioned correctly for all 140 patches with no incorrectly assembled patch entering dosing mode."

The sponsor referenced two clinical studies (NP101-025 and NP101-026) to validate the Pad Detection System. However, the two clinical studies reported several adverse events relating to administration site conditions, including painful burns. Burns under electrodes typically occur due to areas of high focused current delivery. Refer to CDER review memos for discussion of these adverse events.

III Device Description

The following was modified from Ms. Pamidimukkala's review memo dated 7/18/11 (revisions in bold):

The NP101 (trade name: Zelrix Iontophoretic System) is a prescription use, co-packaged drug/device combination iontophoresis product that is intended to deliver sumatriptan transdermally to treat migraine attacks (with and without aura) in adults. The patch is intended to be applied to the upper arm or thigh. The sponsor refers to the device component of the combination product as the E-Patch. The E-Patch is a disposable, nonsterile, single-use transdermal iontophoresis patch. The E-Patch consists of a microcontroller (b) (4) battery, (b) (4) electrode, and overtape. The micro controller is pre-programmed to deliver a set current profile over 4 hours (b) (4). Just prior to use the user assembles the system by attaching the drug and salt imbibed pads to the E-Patch (cathode and anode, respectively). This entire assembly is affixed to the user's skin for iontophoretic drug delivery. The current delivery commences once users depress the ON button for 1.5 seconds.

The patch power supply consists of batteries and programmed micro controller. The device is powered by two (2) (b) (4) batteries that are supplied with the device and housed with the (b) (4) programed micro controller. This power supply is encased in a translucent plastic dome (b) (4)

The dome has a button that users press to activate the patch (patch is shipped and stored in sleep mode) and begin current delivery. The power supply also includes a LED to indicate device status (e.g., in use, sleep mode, etc.). Because the plastic dome is translucent, users can see the batteries and the (b) (4) but they are not able to access the batteries or the circuitry.

The electrode is (b) (4)

(b) (4)

(b) (4) foam encircles the electrodes and (b) (4) rings and provides some structure to the patch. The (b) (4) flexible foam is (b) (4) to adhere to the patient's skin. The top surface of the patch is constructed from cloth woven overtape. The overtape is (b) (4) to adhere to the patient's skin. The (b) (4) foam, overtape, and adhesives are all directly patient contacting.

The device is shipped in Sleep Mode and the LED is off. Users activate the device by pressing the button in the cover dome for a minimum of 1.5 seconds (labeling instructs users to depress and hold the button for 5 seconds). Upon activation the device performs a self-test (b) (4)

(b) (4)

The patch is designed to operate within a range of (b) (4) and voltage delivery is up to (b) (4) VDC for (b) (4). The controller monitors current delivery and adjusts voltage to maintain constant current to compensate for changes to skin impedance during Active Mode. The sponsor has calculated the treatment area as the area of the imbibed pads; 30 cm². This correlates to current density of (b) (4) mA/cm² for (b) (4) and (b) (4) mA/cm² for (b) (4)

Safety Features: Several safety features are built into the firmware programmed onto the microcontroller to protect the patient during the dosing period. They are:

- During the (b) (4) the voltage may be increased up to (b) (4) VDC to overcome high skin resistance. This boost in voltage is limited to a maximum of (b) (4) minutes. The maximum current that may be delivered during this boost is (b) (4) milliamperes.
- If a current of (b) (4) milliamperes is measured for a cumulative (b) (4) minutes during the dosing period the firmware places the E-Patch in Inactive Mode. Current at this level would be measured if the patient had extremely high skin resistance or if the patch was removed before the end of the dosing period.
- During Test Mode or Active Mode if the current exceeds (b) (4) milliamperes for a continuous period not to exceed (b) (4) the firmware places the E-Patch in Inactive Mode.
- During Test Mode or Active Mode if the voltage remains above (b) (4) VDC for a continuous period exceeding (b) (4) the firmware places the device in Inactive Mode.
- The electronics are not capable of delivering more than (b) (4) Watts for more than 1 second as a result of any single fault failure condition.
- **The Pad Detection System (PDS) consists of (b) (4) (b) (4)**

each anode and cathode electrode. (b) (4)

The PDS was designed to prevent NP101 from turning on (i.e., entering active delivery mode) in the event the pads were not correctly aligned or absent, as exposed electrodes during active delivery were associated with unacceptable safety concerns.

The PDS operates in (b) (4) distinct stages, which occur automatically after the patient begins pr (b) (4)

(b) (4)

Appropriate electrical characteristics must be demonstrated for multiple consecutive time points for Stages (b) (4) NP101 will terminate operation (i.e., enter Inactive Mode) if it does not pass Stages (b) (4)

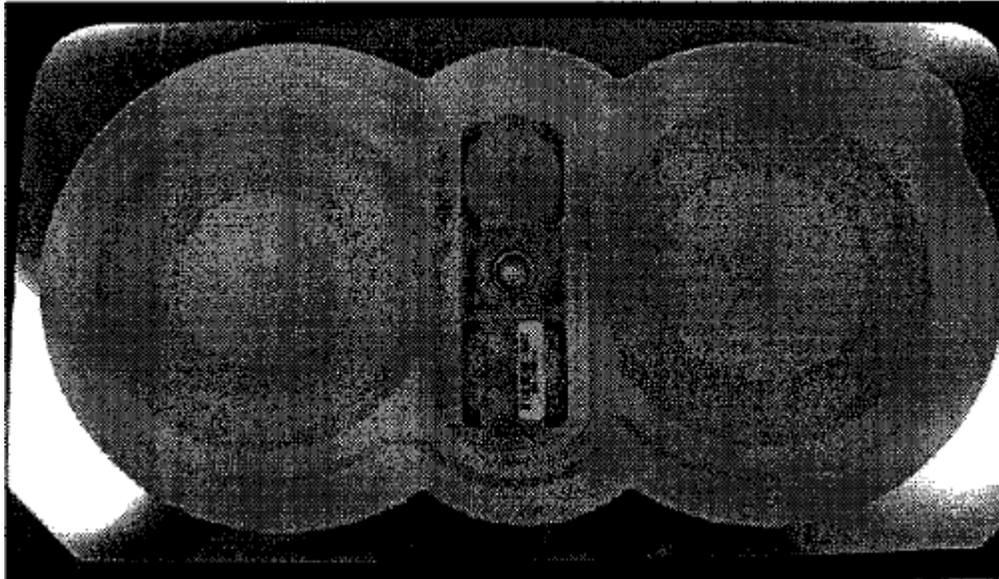


Figure 1: Top view (anode on left): woven overtape and power supply/dome

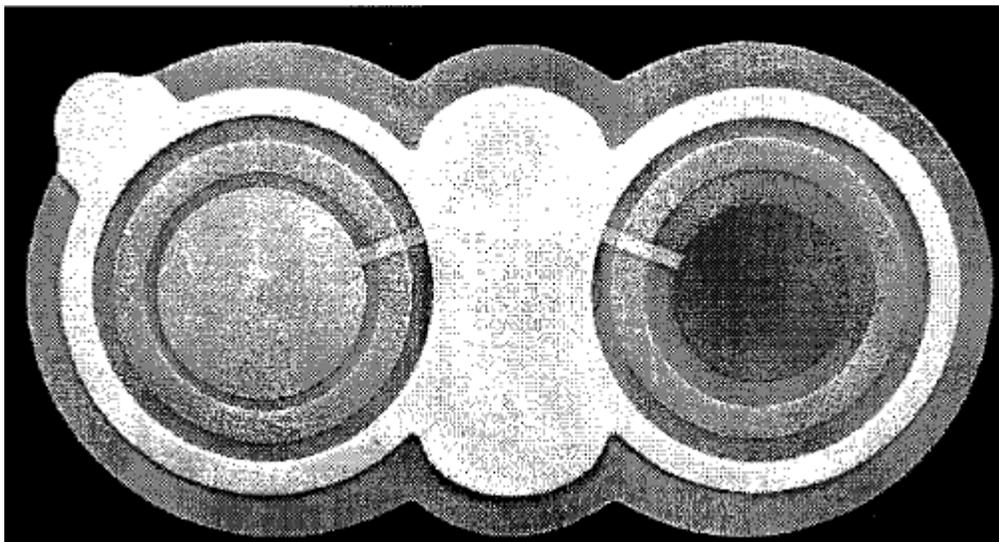


Figure 2: Bottom view (anode on right): electrode, (b) (4) rings, adhesive foam backing

Enhanced Design with PDS

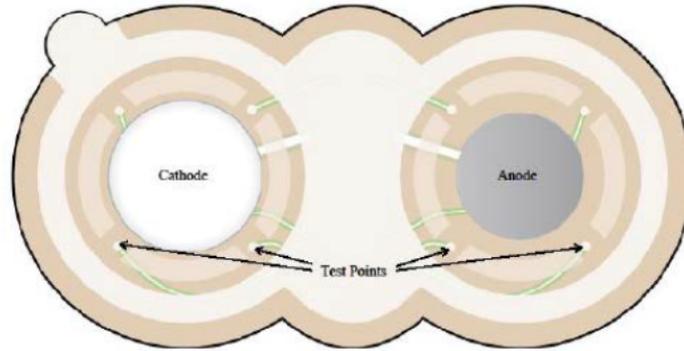


Figure 3: E-Patch with PDS

Table 1: Device Summary

Device Characteristic	NP 101
Electrode material	(b) (4)
Electrode area	(b) (4)
Electrode capacity	(b) (4)
Current delivery profile	(b) (4)
Constant current/voltage	(b) (4)
Max output voltage	(b) (4)
Max output power	(b) (4)
Current density*	(b) (4)
Power density*	(b) (4)
Operational Impedance Range	(b) (4)
Battery <ul style="list-style-type: none"> Type Capacity 	<ul style="list-style-type: none"> two (2) (b) (4) batteries (b) (4) nominal capacity of (b) (4) mA hours, minimum 4 hour runtime
Modes	<ul style="list-style-type: none"> Sleep Mode: { (b) (4) } Test Mode: follows (b) (4)

	<ul style="list-style-type: none"> • <i>Active Mode</i>: follows (b) (4) • <i>Fail Mode (Inactive Mode)</i>: (b) (4)
LED indicator	<ul style="list-style-type: none"> • <i>Sleep Mode</i>: (b) (4) • <i>Test Mode</i>: (b) (4) • <i>Active Mode</i>: solid red • <i>Fail (Inactive) Mode</i>: (b) (4)
Single use	Single use, single patient, disposable
Sterile	Provided and used non-sterile

* The listed current density and power density are calculated by reviewer. The sponsor's provided current density is calculated over the area of the imbibed pads, which is greater than the area of the anode and cathode. As it has not been established that the current is evenly distributed over the entire area of the imbibed pads, I have calculated the current and power densities over the area of the anode and cathode, which would represent a worst-case use of the skin contacting the electrodes directly.

Reviewer Comments

1. The design of the device is unique as compared to most other iontophoresis patches. Typically, iontophoresis patches are significantly smaller than the subject device. The large electrode size and the relatively low current delivered results in lower current and power density values. The calculated values are well below values that would be likely to result in burns or blistering. The sponsor has calculated the current density based on the size of the drug imbibed pads. It should be noted that the imbibed pads are larger than the electrodes and it is unclear if the current is evenly distributed over the entire drug pad, including the area that is not directly contacting the conductive area of the electrode. The sponsor was asked in the day 74 letter to conduct a dispersion test to demonstrate that the current is evenly distributed over the conductive area of the electrode and over the entire area of the drug pad. The current and power density should be calculated over the area on which current is delivered to the patient. FDA recommends that the maximum power density of stimulating electrodes should be less than 250 mW/cm² to reduce the risk of thermal burns. Power density should be calculated using the maximum allowable current for the electrode with the smallest conductive surface area.
2. The system delivers a (b) (4) current in Test Mode to ensure the patch is affixed to the patient before entering Active Mode. Also, Pg. 13 states the system will (b) (4). It is unclear by (b) (4)." What is the delivered test current and why is it not consistent (possibility of higher test current?) **The sponsor states the device will immediately enter Active Mode from Test Mode if the correct current is detected.**
3. **What are the associated pass/fail criteria for each parameters evaluated during the Self Test mode?**
4. **If the device re-enters Sleep Mode following (b) (4)**
5. **The LED indicator for (b) (4)**
How is it possible for a user to differentiate between a device that is in Sleep Mode vs. a device that has entered Fail Mode?
6. The sponsor states that the electrode capacity specification is (b) (4) mA-min minimum.

This is the very minimum electrode capacity needed to achieve the prescribed current profile (b) (4). (refer to TM-0002; capacity test method for NPI01)

7. The imbibed pads are identical in appearance (both are white and are the same size and constructed from the same material). The sponsor should make these pads distinguishable such that a user can identify which pad contains the drug and should be applied to the appropriate electrode. **The sponsor modified the device with the Pad Detection System feature.**

IV Packaging

The following was modified from Ms. Pamidimukkala's review memo dated 7/18/11):

Section 3.2.P.7 of the NDA includes a detailed description of the NP101 packaging. Additional information regarding the container closure system was provided in Amendment 15 (6/15/11) in section 3.2.P.7.

(b) (4)

Packaging and labeling of the final co-

packaged drug/device product will occur at (b) (4)

Primary package: the primary packaging is described by the sponsor as the packaging of the drug product portion, the reservoir card. The primary packaging consists of a bottom foil, upper foil, and the non-woven pads imbibed with salt or sumatriptan formulations. The foil materials have been approved by CDER for blister packaging of oral dosage forms. The imbibed pads are placed on the bottom foil. The upper foil is (b) (4) sealed around the imbibed pads. Refer to the CDER review memos for discussion of primary packaging (Reservoir Card).

(b) (4)



(b) (4)

Market Packaging: The pouches are shipped in cartons constructed from (b) (4). The units are available in (b) (4) 6 pack cartons. The packaging passed the International Safe Transit Association (ISTA) integrity performance test 1C to verify the marketed package can withstand the rigors of the shipping distribution environment without affect to the function of the product.

Reviewer Comments

1. The information regarding the E-Patch packaging is adequate. The packaging of the imbibed pads (i.e., the reservoir card) is reviewed by CDER as the pads are the drug component.
2. Internally, there was some concern of the potential for static from the transparent (b) (4) sheet to affect the (b) (4). The sponsor has completed evaluation of the device per IEC-60601-1 and demonstrated the device is immune to electrostatic discharge.
3. It is worth stating that a previously approved iontophoresis combination product, the lonsys iontophoresis device (NDA 21-338, IND (b) (4)



For the subject device, the potential for circuitry degradation due to excessive moisture within the packaging is unlikely because the imbibed pads with are sealed and contact between the pads and E-Patch is unlikely. Additionally, the sponsor found that high ambient humidity (75% RH) did not affect the performance of the device in the shelf life evaluation.

4. Note, the packaging used for the NP101 clinical evaluations is slightly different than the proposed marketing packaging. A plastic holder was used to hold the E-Patch (b) (4) during the clinical evaluations. This difference is unlikely to impact product safety or effectiveness as the packaging material is inconsequential to the performance of the device. This difference may impact device usability, however. As such, the sponsor has conducted a usability study which is reviewed by CDER.

V Labeling

The following was modified from Ms. Pamidimukkala's review memo dated 7/18/11 (revisions in bold):

The sponsor has provided product labeling in Section 1.14 of the original submission. The product is referred to by its trade name within the labeling: ZELRIX. The labeling contains contraindications, warnings, precautions, and adverse reaction information, but does not differentiate between those associated with the drug and the device. Below is a brief summary of the elements within the labeling that I have identified as being primarily associated with the device component.

- *Indications:* The labeling includes the appropriate indications for use (transdermal delivery of sumatriptan for the acute treatment of migraine attacks, with or without aura, in adults). (b) (4)
- *Administration/Dosing:* (b) (4)
- *Contraindications:* (b) (4)
- *Warnings & Precautions:* (b) (4)
- *Adverse Reactions* (b) (4)
- *Storage info: (section I6) room temperature;* (b) (4)
- *Expiration:* will be labeled with (b) (4) expiration (see shelf life evaluation below)
- Contact info
- Rx use only
- Disposal: There are no specific disposal instructions. The device component can be disposed of in regular household trash.

Patient Labeling begins in section 17.8 of the labeling section. This section includes patient instructions for use.

Reviewer Comments

Please note these were communicated to CDER in Ms. Pamidimukkala's review memo dated 7/18/11, however the following (in bold) were not addressed in the latest version of the labeling.

1. Patient labeling section:

- (b) (4) **It may be worth adding an explanation that if the light turns off before 4 hours the device, the full 6.5 mg may not have been delivered.**

- Under (b) (4)
- This reads that users can have 2 patches active at the same time.**
2. (b) (4)
 3. **Warnings/Precautions:** (b) (4)
 4. For reference, the other NDA approved iontophoresis system IONSYS (NA 21-338) labeling included the following statements:
 - The system should be removed before cardioversion or defibrillation to avoid damage to the system from the strong electromagnetic fields set up by these procedures.
 - Device contains radio-opaque components and may interfere with an X-ray image or CAT scan.
 - The low-level electrical current provided by IONSYSTEM does not result in electromagnetic interference with other electromechanical devices like pacemakers or electrical monitoring equipment.
 - The labeling indicated that the current delivery is generally imperceptible.
 - Instructed not to place patch on abnormal skin sites; scars, bums, tattoos

VI Sterilization & Shelf Life

The following was modified from Ms. Pamidimukkala's review memo dated 7/18/11 (revisions in bold):

Sterility: The NPIOI co-packaged drug/device combination product is not being marketed as a sterile device or system. The device is packaged, supplied, and used non-sterile.

Shelf Life: sponsor states the 6 month real-time stability evaluation in commercial packaging and 9 months real time stability evaluation in clinical packaging supports extrapolation to (b) (4) shelf life from date of manufacture (reference Release Specification document provided in Amendment 0003, 3.2.P.5.1).

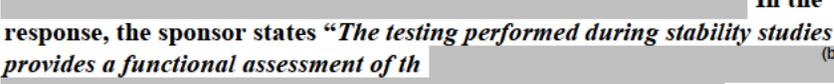
Stability studies are underway with NP101 to address shelf- life. These stability studies are detailed in Section 3.2.P.8 of the NDA.

- Stability data for co-packaged product in commercial packaging is available through 6 months. Section 3.2.P.8.1.4 (original submission) outlines the evaluations of the device performance on the commercially packaged system evaluated over 6 month time period. Samples evaluated at initial release, 1,2,3, and 6 months at accelerated (40oC/ 75% RH), CRT (25 oC/60% RH) at initial, 3 and 6 months, and intermediate (30 oC/ 65% RH) at initial and 6 months. The sponsor evaluated the (b) (4) (per NuPathe method TM-0002) and (b) (4) (per SOP CM 013) of the device component to demonstrate that the device performance is unaffected by storage. All testing met specifications. Evaluated Lot #: MBR-75-NPIOI-017-0001
- Stability data for co-packaged product in clinical packaging is available through 9 months. Section 3.2.P.8.1.5 (original submission) outlines the evaluations of the device performance on the clinically packaged system evaluated over 9 months. Samples were evaluated at 3 and 6 months at accelerated (40 oC/ 75% RH). Samples were evaluated at initial, 3, 6, and 9 months with CRT (25 oC/ 60% RH). Samples were evaluated at intermediate conditions (30 oC/ 65% RH) at 6 and 9 months (b) (4) were tested at each evaluated time point. All testing met specifications. Evaluated Lot #: MBR -75-NP101-007-0012.

Amendment 16 (6/21/ 11)- the sponsor provided a (b) (4) report to demonstrate that the storage orientation (flat, side, etc.) does not have a material impact on pad saturation or drying. The provided information is adequate.

Reviewer Comments

1. The conducted shelf life testing on the clinical and commercially packaged system (9 months and 6 months, respectively) can be used to support an expiration date of (b) (4) months, however the sponsor should address the following:
 - NuPathe Stability Protocol for NP101 Documents for Device Stability, Lot MBR-75-NPIOI-007-0012 and Lot MBR-75-NPIOI-01 7-0001 (Document Nos: Prot-CM-NP101-007, and Prot-CM-NP101-008, respectively) state the protocol was amended to (b) (4)

In the response, the sponsor states “The testing performed during stability studies provides a functional assessment of th (b) (4)

.” In Section (b) (4)
3.2.R.4.4.5.4, the sponsor states “

.”
 - **The sponsor provided the pass/fail criteria for the** (b) (4)
 **test.**

Note- the sponsor also evaluated the drug reservoir stability and the adhesive stability. These evaluations were reviewed by CDER.

2. It is worth stating that the actual age of the lot for the Reservoir Card that was evaluated in the co-packaged stability studies (both clinical and commercial) was greater than that at the time of the pull. (12 months for clinical, 15 months in commercial). This does not affect the device performance evaluations because the reservoir card was not utilized in the device performance tests. The sponsor evaluated only the electrode capacity and the current delivery profile over 4 hours. In both the clinical and commercial co-packaged evaluations, the performance of the device met acceptance criteria. It is anticipated that because the sponsor has demonstrated that electrode charge capacity is unchanged and the device is able to consistently deliver current appropriately over the 4 hour delivery time, the device will be unaffected by storage. The shelf life evaluations are acceptable.

VII Biocompatibility

The following was modified from Ms. Pamidimukkala’s review memo dated 7/18/11 (revisions in bold):

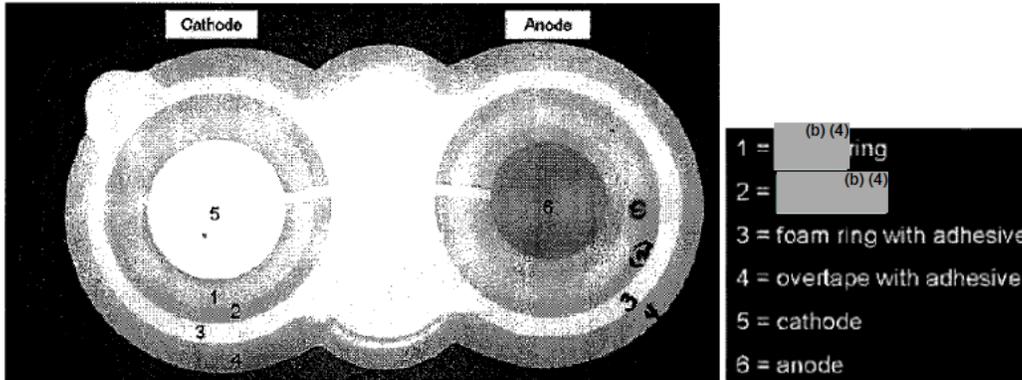
The sponsor has identified the following materials used in construction of the E-Patch as having direct contact to the patient:

- (b) (4) adhesives (b) (4) the foam and the overtape.
- Foam
- Overtape
- (b) (4) film
- (b) (4) pad transfer ring

According to ANSI/ AAMI/ISO 10993-1:2003 Table 1, the E-Patch is considered a skin surface contacting device with limited contact duration. As such, all patient contacting components of the patch should be evaluated for cytotoxicity, sensitization, and irritation or intracutaneous reactivity. Biocompatibility studies that have been performed with the foam, overtape, (b) (4) film, and (b) (4) pad transfer rings. The test article was identified in each report as the E-Patch (with (b) (4) removed). Testing of (b) (4) (b) (4) pad transfer ring (b) (4) ring), overtape with adhesive (b) (4) and foam. The tests were conducted at an independent contract laboratory. The tests were performed under GLP regulations (21 CFR 58) and in accordance to SOP and a standard protocol. All biocompatibility reports are located in the Toxicology section of the original NDA submission (section 4.2.3.7.7). Complete reports were provided for the following assays:

- *Cytotoxicity*: ISO 10993-5:1999- "Biological Evaluation of Medical Devices, Part 5: Tests for in vitro cytotoxicity." The assay evaluated the in vitro toxicity of the test article to mammalian cells when leachable extracts were allowed to diffuse through an agarose barrier and contact cultured cells. L-929 mouse fibroblast cells were utilized for this assay. The positive control, negative control, and test articles (1 cm x 1 cm) were placed in the agarose culture in triplicate and incubated for 24 hours. The control samples and test articles were removed from the culture and the culture was stained and evaluated for cell lysis. The test article showed no signs of lysis under or around the test area (score 0). The positive control had a score of 4 (toxic) and the negative control had a score of 0 (non-toxic). The results are valid.
- *Irritation*: ISO 10993-10:2002- "Biological Evaluation of Medical Devices, Part 10- Tests for irritation and sensitization"- test article and negative control patches (6 of each) were applied to the shaved skin of 3 adult albino rabbits for four hours. Observations for skin irritation were conducted at 60 minutes, 24 hours, 48 hours, and 72 hours after removal of patches. One animal had a score of 1 (very slight erythema) at the 24 hour mark on the right side. This resulted in a primary irritation score of 0.2 for this animal. The overall primary irritation score for the test article is 0.1, which is negligible. The results conclude that the test article elicits negligible irritation response.
- *Dermal Sensitization*: ISO 10993-10:2002 "Biological Evaluation of Medical Devices- Part 10: tests for irritation and delayed type hypersensitivity" Repeated Patch Dermal Sensitization Test (Buehler method, modified for longer induction exposure for test article). 10 guinea pigs patched with test article, 5 guinea pigs patched with negative control for 6 hours of exposure followed by 24 hour rest period and observed for erythema and edema. The procedure was repeated 3 times per week for 3 weeks (total of 9 applications). Following a 2 week rest period the animals were patched with the respective test article (test article on test animals and control article on control animals). The patches were removed after 6 hours exposure. Patch sites were observed for erythema and edema at 24 hours and 48 hours after patch removal.

Geeta discussed the completed tests with Joseph Neilsen, PhD, the biocompatibility expert in CDRH/ODE/DSORD. He determined that the completed testing is adequate. A formal consult was not requested.



Reviewer Comments

1. The test article in each report is described as the "E-Patch (with (b)(4) removed); testing (b)(4) pad transfer ring, overtape with adhesive, foam barrier with adhesive." A discussion with Joseph Nielsen, PhD, the biocompatibility expert in CDRH/ODE/DSORD concurred that the biocompatibility testing for this adequate.
2. **The sponsor states "To allow for (b)(4), the adhesive used for the pad transfer rings was changed to (b)(4) Adhesive. Biocompatibility test reports are provided in Section 3.2.R.4.4.4."** During a CDER Internal Review Meeting on December 3, 2012, it was noted that this adhesive for the pad transfer rings was not a patient-contacting device component.
3. Please note there were reports of several adverse events relating to administration site conditions (e.g., itching, stinging, rash) in three clinical studies (i.e., NP101-024, NP101-025, NP101-026). Refer to CDER review memos for discussion of these adverse events.

VIII Software & Firmware

The following was modified from Ms. Pamidimukkala's review memo dated 7/18/11 (revisions in bold):

The device uses firmware preprogrammed onto the micro controller. The firmware cannot be modified or accessed by the patients or physicians. The sponsor has identified the firmware as having a major level of concern because it is intended to be used in combination with a drug. The microcontroller is (b)(4) t. The firmware is written using (b)(4) code. The purpose of the firmware is to control the delivery of current over the set 4 hour dosing period.

The software (firmware) is determined to have a MAJOR level of concern because the device is intended to be used in combination with a drug. Note, the release version of the firmware is Version (b)(4).

The firmware controls the following functions (as described in the SRS (attachment 18) document in the original submission):

- Sleep Mode - (b)(4)
- Self-Test- (b)(4)

- Test Mode - (b) (4)
- Active Mode - (b) (4)
- System Timing - (b) (4)
- Current delivery - (b) (4)
- Self-Test Fail Mode - (b) (4)
- (b) (4)
- (b) (4)

The sponsor has provided all applicable software documentation in section 8 of 3.2.R.4 of the original submission. Per CDRH Guidance document for the Content of Pre market Submissions for Software Contained in Medical Devices, the sponsor has provided the following documentation for devices that contain software having a MAJOR level of concern:

- Software Requirements Specifications (SRS): (attachment 18: software requirements specification review report)- the sponsor provided the SRS document (with amendments) for the functional requirements for each mode: sleep mode, self-test, test mode, active mode, and self-test fail mode. The SRS Review Report notes the fixes for anomalies observed in software version (b) (4). There are no unresolved anomalies.
- Architecture Design Chart: (attachment 19)- the sponsor provided an adequately detailed Software Architecture Design Document (SADD)- which incorporates the SDS documentation. The sponsor has provided state flow charts. There are some minor typographical errors that were noted in the document that will be addressed after updates. There are no unresolved anomalies noted.
- Software Design Specification (SDS) (attachment 19)- the sponsor has combined the SDS and architecture design chart into 1 document which they refer to as SADD. The document includes detailed description of the software modules/states and includes code for each state. Note- speed up mode is used during testing and not available during clinical use.

- Traceability Analysis: (attachments 20, 21, 22)- the sponsor provided multiple traceability documents. Attachment 20: lining SRS to the test case and test procedures documents. Attachment 21: lining SADD to Source Code Verification document. Attachment 22: lining software hazards to SADD (see Hazard Analysis section of memo below).
- Software Development Environment Description: In section 8.8 of 3.2.R.4 (original) the sponsor outlines the software development process. The firm used an evolutionary development strategy; continually modifying the software during the development process as new requirements and safety factors were identified. Clinical evaluation of the software was initiated only following satisfactory evaluation in bench evaluations. Subsequent modifications were made following new issues identified during clinical use. The microcontroller had undergone 4 generational changes.
- Verification & Validation: The sponsor provided the test procedure and log for all completed V&V evaluations. It is not clear if all V & V evaluations were conducted on the system version to be commercially available.
- Revision Level History: The sponsor provided a memo in attachment 48 from (b) (4) the firm contracted to develop and test the software, which states the final version of the software is version (b) (4). The memo also states that the modification made in (b) (4) from version (b) (4) was a change in (b) (4) (change removed (b) (4)). The change was prompted by the microprocessor which is designed with (b) (4). The change does not affect operation of the device and the completed validation on version (b) (4) is applicable to version (b) (4). Version (b) (4) was only evaluated per the Fast test and the 4-Hour test.
- Unresolved Anomalies: The sponsor states there are no unresolved anomalies in release version (b) (4).

Reviewer Comments	
1.	How many times can the patch enter sleep mode (b) (4)
2.	The sponsor states “The final version of firmware in the proposed to be marketed product is (b) (4). Verification and validation of this final firmware version is discussed more specifically in Section 3.2.R.4.2.7.” However, the Verification and Validation documentation of this final firmware version in Section 3.2.R.4.2.7 does not provide a complete description of the validation and verification activities at the unit, integration, and system level. Therefore, the sponsor should provide unit, integration, and system level test protocol, including pass/fail criteria, test report, summary, and test results.
3.	The sponsor should also provide further details of the (b) (4)

IX Electromagnetic Compatibility and Electrical, Mechanical and Thermal Safety

The following was modified from Ms. Pamidimukkala’s review memo dated 7/18/11 (revisions in bold):

In section 2 of 3.2.R.4 (original submission) the sponsor declares conformity to the following electrical safety standards.

- IEC 60601- 1 -2 (2001): Medical Electrical Equipment- Par 1: General requirements for safety; Electromagnetic compatibility requirements and tests.
Electromagnetic Compatibility evaluation was conducted by a contract lab; (b) (4). The test report was included in Attachment 49. The report evaluated the following:
 - Radiated Emissions: IEC 60601-1-1 (2007) Group 1 Class B
 - Electrostatic Discharge: IEC 61000-4-2 (2008)
 - Radiated Immunity: IEC 61000-4-3 (2008)
 - Magnetic Immunity: IEC 61000-4-8 (2009)

- IEC 60601-2-2 (2006): Medical electrical Equipment- Part2-2: Particular requirements for the safety of high frequency surgical equipment

Reviewer Comments

- 1. The sponsor provided conformability testing per IEC 60601-2-2 standard for the 4-hour application time.**

X Performance Testing

The following was modified from Ms. Pamidimukkala's review memo dated 7/18/11 (revisions in bold):

A Bench

- Power supply performance verification (Attachment 50)- variable resistance, maximum resistance conditions to evaluate correct device output and performance. This test is conducted to verify power supply performance.
- **Power Source Verification (1107286-000-e0t0-0612-bjm1): evaluation of battery performance. Battery should meet pre-specified power and capacity requirements (based on power requirements for proper device performance). Based on the results obtained from testing described in the report, recently manufactured unused (b) (4) cells meet all of the power, capacity, and runtime requirements under the highest power drain conditions specified for the E-Patch device operation.**
- Electrochemical capacity of electrodes (amendment 7, Doc # TM-0002.04)- evaluation of anode and cathode electrode capacity to ensure the electrodes will be able to have at a minimum capacity of (b) (4) mA-min to ensure proper use of the device.
- Conformability (attachment 55)- at the request of FDA (during pre-NDA meeting 3/4/2010) requesting evaluation of the patch conformability to thigh and arm. During this meeting Geeta suggested the firm reference ANSI/AAMI HF 18 for guidance in method development. That standard is no longer recognized by the Agency and is superseded by IEC 60601-2-2. The sponsor used this standard for test method development. The standard evaluated conformability to user forearm for worst case (5 females, 5 males). The patch was left on the arm for 1 hours. All patches had less than (b) (4) lift. **In a clinical study, NP101-024, the patch was left on the upper arm and forearm in 6 females and 6 males for 4 hours. All patches had less than (b) (4) % lift.**
- Current Density: in the Day 74 letter, Geeta had requested the sponsor complete a dispersion test or equivalent to ensure that the current is evenly distributed over the area of the electrodes and that there is no area of unintended focal current during normal current delivery that could result in burn or injury to the user. The sponsor responded with FEA models for 3 scenarios: 1) intended use (where drug pad and salt pad completely cover the anode and cathode, respectively), 2) unintended use # 1 (where the device is operated without the pads; anode and cathode directly contact the skin), 3) unintended use #2 (where drug pad and salt pad are misaligned; 25% of each electrode is in direct contact with skin). It was determined that the highest degree of non-uniform current density distribution occurs at (b) (4) Q, with decreasing non-uniformity as contact resistance increases. Models revealed that current density is non-uniform between anode/drug pad and cathode/salt pad surfaces (with increasing current density towards outer edge of electrode). The non-uniform distribution is less evident at the skin surface.

B Animal

The sponsor conducted several dermal tolerance evaluations using pig model.

C Clinical

Pivotal study with 530 human subjects, multi-center, randomized, parallel group, double blind, placebo controlled trial established efficacy and tolerability. The clinical studies were evaluated by CDER.

Reviewer Comments

1. The completed bench tests are adequate. The performance of the device has been adequately verified.
2. The completed FEA modeling evaluation of current density distribution is adequate. It is common to see increased current density at the outer edges of the electrodes. The limitations of the maximum current reduce the likelihood of this non-uniform distribution to result in patient injury. **Therefore, the sponsor should conduct an evaluation of the current density distribution of the device in use for complete and incomplete patch adherence scenarios. In addition, the sponsor should provide a discussion on scenarios that would result in burns using the device.**
3. The use of the pig model for the animal tolerance tests is adequate. The pig model is frequently used as animal model for human skin, particularly for RF dermatological evaluations.
4. The clinical study reports were evaluated within CDER. I reviewed these reports and found that the most commonly occurring adverse events (site pain, site pruritus) are typical for iontophoresis devices.

XI Hazard Analysis

The following was modified from Ms. Pamidimukkala's review memo dated 7/18/11 (revisions in bold):

The device hazard analysis (Attachment 17: Software Safety Report and Review Report) was performed by (b) (4) during the verification and validation of the firmware. ISO 14971:2007, "Medical Devices - Application of Risk Management to Medical Devices," and IEC 62304:2006, "Medical Device Software - Software Life Cycle Processes" were referenced for the analysis.

Reviewer Comments

1. **The provided hazard analysis is incomplete and inadequate. However, the analysis did not fully evaluate the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards. Therefore, the sponsor should update the hazard analysis to include a description of all potential hazards (e.g., electrical, operational, environmental, mechanical) presented by this device, the causes and severity of the hazards, the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards.**

XII Deficiencies to be Conveyed to the Sponsor

1. In your response to Deficiency 46b in our Additional Information request dated July 15, 2011, you reference Section 3.2.R.4.2.3.3 of your submission, which describe the (b) (4) (b) (4) f. However, you did not provide a detailed description of this mode. Please provide a description of the (b) (4) mode, including the method of (b) (4)
2. In your response to Deficiency 47a in our Additional Information request dated July 15, 2011, you state "the Self-Test mode verifies battery voltage meets the minimum threshold for activation and verifies electronics functionality." You provided the Self-Test Mode Flowchart in Figure 9 of Section 3.2.R.4.2.4.1.3 of your submission. Figure 9 indicates (b) (4)

3. In your response to Deficiency 47d in our Additional Information request dated July 15, 2011, you state “ (b) (4)

” In the Architecture Design Chart, the device enters Inactive Mode followin (b) (4)

Therefore, please address the following:

- a. Clarify how the device (b) (4)

- b. The LED indicator for (b) (4)
Please indicate how is it possible for a user to differentiate between a device that is in Sleep Mode versus a device that has entered Fail Mode.

4. In your response to Deficiency 47e in our Additional Information request dated July 15, 2011, you reference Section 3.2.R.4.2.3.4 of your submission, which states (b) (4)

There appears to be inconsistency in the current profile of your device. Please ify why (b) (4)

5. In your response to Deficiency 48a in our Additional Information request dated July 15, 2011, you provided a revised hazard analysis in the REP-DHF-NP101-296 report. However, the analysis is incomplete as it did not fully evaluate the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards. Therefore, please update the hazard analysis to include a description of all potential hazards (e.g., electrical, operational, environmental, mechanical) presented by this device, the causes and severity of the hazards, the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards.

Note: This is typically done in an enumerated columnar form, wherein the first column identifies the hazard to the patient, the second column identifies from where in the system that hazard could be caused, the third column presents, for software caused hazards, where in the software the hazard could be caused, the fourth column provides the specific details of the mitigation including identifying the enumerated tests, and the fifth column identifies any residual hazards.

6. In your response to Deficiency 49 in our Additional Information request dated July 15, 2011, you state “*The final version of firmware in the proposed to be marketed product is* (b) (4). *Verification and validation of this final firmware version is discussed more specifically in Section 3.2.R.4.2.7.*” However, the Verification and Validation documentation of this final firmware version in Section 3.2.R.4.2.7 does not provide a complete description of the validation and verification activities at the unit, integration, and system level. Therefore, please provide unit, integration, and system level test protocol, including pass/fail criteria, test report, summary, and test results.

Labeling

7. The Patient labeling section includes the following statement; (b) (4)

(b) (4) Please add a statement explaining that if the light turns off before 4 hours, the full 6.5 mg sumatriptan may not have been delivered.

8. In the Patient Labeling section under the "How should I use ZELRIX" heading, states (b) (4)
This statement can be interpreted to mean users can apply 2 active patches simultaneously. Please revise this statement to make clear that users may apply a second patch following shut down of the first patch.
9. Please add the following contraindication: for patients with known sensitivity or adverse reaction to application of electrical current
10. Please add the following to the Warnings/Precautions sections of your labeling: "patch can be worn during normal activity, however excessive motion may cause poor contact between skin and electrodes. This may result in uneven distribution of current increasing the risk of skin irritation." Additionally, please add a statement instructing users to remove the patch if they experience a burning sensation during use.

XIII Contact History

None

XIV Recommendation

I recommend an AI letter to be sent to the sponsor with the deficiencies listed above.

Lead Reviewer Signoff:

Katherine Kim, Biomedical Engineer (ODE/DNPMD/PNDB)

Management Sign off (when applicable):

Branch Level _____
Quynh Hoang, Acting Branch Chief (ODE/ DNPMD/PNDB)

Date _____, Concur: Yes No

Division Level _____

Date _____, Concur: Yes No

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

/s/

LANA Y CHEN
12/10/2012
placed in DARRTS for CDRH

Site(s)

(b) (4)

(b) (4)

Requires Inspection? Y N
Site ready for inspection? Y N
N/A

If no, add date site will be ready:

(b) (4)

(b) (4)

Requires Inspection? Y N
Site ready for inspection? Y N
N/A

If no, add date site will be ready:

(b) (4)

Requires Inspection? Y N
Site ready for inspection? Y N
N/A

If no, add date site will be ready:

DEVICE:

**Sumatripan Iontophoretic Transdermal System /
Zecurity (Previously Zelrix)**

RECOMMENDATION: *Information inadequate – Send Deficiency Letter.*

INTENDED USE:

Acute treatment of migraine attacks, with or without aura, in adults.

DEVICE DESCRIPTION:

Zelrix™ is a disposable, single-use, co-packaged drug/device combination product that utilizes iontophoretic technology to deliver sumatriptan transdermally for the treatment of acute migraine attacks.

Iontophoresis is a non-invasive drug delivery method that uses low electrical current to move ionized drugs across the skin to the underlying tissue and blood vessels.

INSPECTION HISTORY (MANUFACTURER AND/OR CONTRACT MANUFACTURER SITE(S)):

This is an NDA, CDER has lead and should cover this section.

CORRESPONDENCE HISTORY:

The firm was not contacted during this review.

FIRM CONTACT (US ADDRESS ONLY):

Michele A. Roy, RN, MS
NuPathe, Inc,
227 Washington Street,
Suite 200
Conshohocken, PA 19428

SECTION I: DESIGN CONTROL INFORMATION:

Design Control, General, CFR 820.30(a)

The firm provided SOP QS-003: Design Control and Pharmaceutical Development (rev .03) which covers their design control procedures. Initial research and development studies for the device component of NP101 (The Electrode Patch) were performed under a developmental license with (b) (4) On January 1, 2007, the research and development agreement with (b) (4) ended, and the product development came under the NuPathe's design control program.

The SOP QS-003 procedure covers new product development and product changes. It states that if (b) (4)

[REDACTED] (b) (4)

The SOP QS-003 procedure discusses responsibilities for design projects, including a [REDACTED] (b) (4). The [REDACTED] (b) (4) is responsible for [REDACTED] (b) (4)

[REDACTED]. It is not clear if this is at all related to validation or verification, but that is reviewed later on in this memo.

The SOP QS-003 procedure also defines the expected 21 CFR 820.30 parts of design control.

The SOP QS-003 procedure describes the processes of [REDACTED] (b) (4)

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.30(a).

Design and Development Planning, 820.30(b)

The firm provided rep-dhf-np101-079.pdf - a development plan in chart form for development of the Zelrix Patch. The form appears to assign responsible resources (as initials). Each part of the design process appears clearly marked and identifiable. Design reviews are noted.

The "device-info-amend-3-14-2011.pdf" document found in Amendment 7 (3/17/11) contains further information to decode the provided development plan. It notes design inputs and sources of the design inputs. It also notes that the [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.30(b).

Design Input, 820.30(c)

The firm provided SOP QS-003: Design Control and Pharmaceutical Development, Section 4.3: Design Input. Form F-QS-008, Design Input/Output and Design Verification was also provided.

DEFICIENCY 1:

You provided SOP QS-003: Design Control and Pharmaceutical Development, Revision .03, in order to satisfy the requirements of 21 CFR 820.30(c), Design Input. In this document, you define Design Inputs and providing the (b) (4)

[Redacted]

DEFICIENCY 2:

You provided SOP QS-003: Design Control and Pharmaceutical Development, Revision .03, in order to satisfy the requirements of 21 CFR 820.30(c), Design Input. In your submission, you state that this procedure addresses (b) (4)

[Redacted]

RESPONSE TO DEFICIENCY 1 and 2:

The firm provided a response to Deficiency 1 and 2 (Item #55) on page 23 of the overall response summary. NuPathe has (b) (4)

two SOPs – SOP QS-003 and the new SOP QS-017 (b) (4) Section 6.3 of SOP QS-017 specifies that (b) (4)

Section 6.3, (b) (4) (820.30(c)) is located on page 8 of SOP QS-017, Rev 1. The first bullet describing specific (b) (4) states “ (b) (4) ”. The procedure also states, on page 24, that “ (b) (4) ”.

[Redacted]

The response appears adequate.

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.30(c).

Design Output, 820.30(d)

The firm provided SOP QS-003: Design Control and Pharmaceutical Development, Section 4.4 – Design Output. The design outputs specific to the E-Patch are described in the "device-info-amend-3-14-2011.pdf" document found in Amendment 7 (3/17/11), Section 1.4. The firm lists (b) (4)

DEFICIENCY 3

You provided SOP QS-003: Design Control and Pharmaceutical Development, Revision .03, in order to satisfy the requirements of 21 CFR 820.30(d), Design Output. In this procedure, you describe (b) (4)

RESPONSE TO DEFICIENCY 3

The firm provided a response to Deficiency 3 (Item #56) on page 23 of the overall response summary. NuPathe has (b) (4)

(b) (4). Section 6.4 of this procedure describes

Section 6.4, Design Output (820.30(d)) is located on page 9 of SOP QS-017, Rev 1. The section states (b) (4)

(b) (4). The procedure goes on to describe (b) (4)

(b) (4). Form F-QS-008 is referenced for documentation of design activities.

The response appears adequate.

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.30(d).

Design Review, 820.30(e)

The firm provided SOP QS-003: Design Control and Pharmaceutical Development, Section 4.5 – Design Reviews. The design review information specific to the E-Patch are described in the "device-info-amend-3-14-2011.pdf" document found in Amendment 7 (3/17/11), Section 1.5. The procedures state

(b) (4)

(b) (4)

(b) (4)

DEFICIENCY 4

You provided SOP QS-003: Design Control and Pharmaceutical Development, Revision .03, and (b) (4) in order to satisfy the requirements of 21 CFR 820.30(e), Design Review. SOP QS-003, section 4.5 explains that the Project Team will

(b) (4)

DEFICIENCY 5

You provided SOP QS-003: Design Control and Pharmaceutical Development, Revision .03, and (b) (4) in order to satisfy the requirements of 21 CFR 820.30(e), Design Review. In (b) (4)

(b) (4)

RESPONSE TO DEFICIENCIES 4 and 5

The firm provided a response to Deficiency 4 and 5 (Item #57) on page 24 of the overall response summary. NuPathe has (b) (4)

[Redacted]

Section 6.4, Design Review (820.30(e)) is located on page 10 of SOP QS-017, Rev 1. The (b) (4)

[Redacted]

Section 5.5 of the SOP states (b) (4)

The response appears adequate.

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.30(e).

Design Verification, 820.30(f)

The firm provided SOP QS-003: Design Control and Pharmaceutical Development, Section 4.6 – Design Reviews. The design review information specific to the E-Patch are described in the “device-info-amend-3-14-2011.pdf” document found in Amendment 7 (3/17/11), Section 1.6. The SOP explains that (b) (4)

[Redacted]

The “device-info-amend-3-14-2011.pdf”, section 1.4, describes design verifications below:

[Redacted]

applied. As stated in NuPathe's response to this request for information (Section 1.11.4.1.8 Multiple Module Information Amendment of the NDA), this information will be provided in an update by the end of March 2011.

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.30(f).

Design Validation, 820.30(g)

The firm provided the following documentation to satisfy 820.30(g), Design Validation.

1. SOP QS-003: Design Control and Pharmaceutical Development, Section 3.10 and Section 4.10 titled Design Validation
2. SOP QS-009: Risk Management Procedure
3. Section 3.2.R.4 of the NDA.
4. Section 3.2.R.4.8 of the NDA – relating to Software validation.

5. Sections 5.3.1.1, 5.3.1.2, and 5.3.5.1 – Clinical Trial Reports.

SOP QS-003 section 3.10 defines [REDACTED] (b) (4)

SOP QS-003 section 4.10 states that [REDACTED] (b) (4)

DEFICIENCY 6

You provided SOP QS-003: Design Control and Pharmaceutical Development, Revision .03 in order to satisfy the requirements of 21 CFR 820.30(g), Design Validation. In this SOP, you define what Design Validation [REDACTED] (b) (4)

[REDACTED] (b) (4)

Please provide an updated Design Control Procedure that clearly defines how design validation activities are to be documented in your [REDACTED] (b) (4),

RESPONSE TO DEFICIENCY 6

The firm provided a response to Deficiency 6 (Item 58) on page 24 of the overall response summary. Section 6.7 of the new SOP QS-017 [REDACTED] (b) (4)

Section 6.7, Design Validation (820.30(g)), is found on page 12 of SOP QS-017, Rev 1. The section states that "[REDACTED] (b) (4)

The response appears adequate.

The firm provided Section 3.2.R.4 to demonstrate completed design validation. Section 3, Executive Summary, the firm states that initial clinical studies showed potential for the delivery method to be efficacious, and resulted in the firm optimizing the current waveform to improve delivery of the drug. A pivotal study

was performed in 530 human subjects in a multi-center, randomized, parallel group, double-blind, placebo controlled trial where efficacy and tolerability of the treatment was compared with the placebo.

DEFICIENCY 7

Your provided section 3.2.R.4, Device (NP101 Electrode Patch) in your NDA submission in order to satisfy requirements of 21 CFR 820.30(g), Design Validation. In Section 3 – Executive Summary, you describe initial clinical tests and a pivotal study. However, it is not clear from this summary how the study results ensure that the device meets user needs and intended uses. Please provide a summary of how your clinical evaluations demonstrated that the device meets user needs and intended uses.

RESPONSE TO DEFICIENCY 7

The firm provided a response to Deficiency 7 (Item 71) on page 32 of the overall summary response. The firm provides a firmware validation in Section 3.2.R.4.2.7.2. NuPathe states that Section 3.2.R.4.4.5.3 describes the clinical performance testing of NP101, Table 4 provides a list of the clinical studies that verified the primary user input, delivering a therapeutic level of sumatriptan over a for hour dosing period, was achieved and maintained.

Section 3.2.R.4.2.7.2, Firmware Verification and Validation, was provided for review. Software verification of the final firmware version – (b) (4) was fully tested for all verification requirements.

Verification activities consisted of reviews and dynamic testing. (b) (4)

[Redacted]

Patient use and device functionality was validated in unit testing and a clinical study (NP101-026). NuPathe states that 100% of any type of use error was detected.

The response appears adequate.

The E-Patch contains firmware that controls the administration of the drug – it executes a sleep mode, start test, test mode, active mode, controls system timing, current delivery, self test fail mode, and (b) (4) mode. The firm states that this causes the software to be a major concern, and conducted testing to match that level.

Early clinical studies used a pre-production version of the microcontroller. The controller was replaced by one from a different supplier for further clinical testing. After this, final development included incorporating additional safety protections and reorganizing the firmware code to allow for verification and validation by (b) (4). After Verification and Validation, the code was updated, and reverified and revalidated. The final release changed (b) (4) which had not been factory calibrated. (b) (4) determined that a subsequent Validation and Verification were not necessary due to this (b) (4) change. The rationale for not conducting the verification and validation for this change is documented in Attachment 48: Memo: Verification Impacts of Version (b) (4) of the Patch Software.

DEFICIENCY 8

You provided Section 3.2.R.4: Software in your NDA submission, in order to satisfy software validation requirements of 21 CFR 820.30(g). In section 8.8. Software Development Environment Description, you describe that version (b) (4) of your microcontroller and firmware were used for initial clinical studies demonstrating feasibility, version (b) (4) were used for further clinical testing, while the production version of the firmware is version (b) (4). However, clinical testing demonstrating validation of version (b) (4) to user needs and intended uses, or information demonstrating functional equivalency of the final firmware version (b) (4) to clinically tested versions (b) (4) could not be located in your submission. Please provide documentation that demonstrates that the E-Patch device with the final firmware version has been validated to user needs and intended uses.

RESPONSE TO DEFICIENCY 8

The firm provided a response to Deficiency 8 (Item #71) on page 32 of the overall response summary. NuPathe states that Section 3.2.R.4.2.5 outlines the development of the firmware for NP101. (b) (4)

Section 3.2.R.4.2.5 – Revision Level History, summarizes the development process for the NP101 firmware. Firmware version (b) (4) was the first to undergo verification and validation activities. (b) (4) was the first version to meet the software verification and validation requirements. For the clinical trial, version (b) (4) was used and only added (b) (4) from version (b) (4) to detect (b) (4) which fixed

(b) (4)

DEFICIENCY 9

You provided SOP QS-003: Design Control and Pharmaceutical Development, sections 3.9 and 4.9 in order to satisfy the requirements of 21 CFR 820.30(h), Design Transfer. In this procedure, you state that design transfer (b) (4)

However, the procedure does not describe how the outcome of the (b) (4)

DEFICIENCY 10

You provided SOP QS-003: Design Control and Pharmaceutical Development, sections 3.9 and 4.9 in order to satisfy the requirements of 21 CFR 820.30(h), Design Transfer. In this procedure, you state that design transfer activities must (b) (4)

RESPONSE TO DEFICIENCIES 9 and 10

The firm provided a response to Deficiencies 9 and 10 (Item #59) on page 25 of the overall response summary. NuPathe has (b) (4)

Section 6.8, Design Transfer (820.30(h)), is located on page 13 of SOP QS-017, Rev 1. The procedure defines (b) (4)

It also states that (b) (4)

The (b) (4) description appears complete.

The response appears adequate.

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.30(h).

Design Changes, 820.30(i)

The firm provided SOP QS-003: Design Control and Pharmaceutical Development, sections 4.11 to satisfy the requirements of 21 CFR 820.30(i), Design Changes.

Section 4.11, Design Changes, states that  (b) (4)







DEFICIENCY 11

You have provided SOP QS-003: Design Control and Pharmaceutical Development, section 4.11 to satisfy the requirements of 21 CFR 820.30(i), Design Changes. In this procedure, you state that  (b) (4)



DEFICIENCY 12

You have provided SOP QS-003: Design Control and Pharmaceutical Development, section 4.11 to satisfy the requirements of 21 CFR 820.30(i), Design Changes. In this procedure, you state that  (b) (4)



DEFICIENCY 13

You have provided SOP QS-003: Design Control and Pharmaceutical Development, section 4.11 to satisfy the requirements of 21 CFR 820.30(i), Design Changes. The procedure should describe when verification is used for certain design changes instead of (b) (4)

However, this information could not be located in your submission. Please provide a procedure that describes how design changes will be determined to require (b) (4), how this is to be documented, and who is responsible for reviewing and improving design changes.

RESPONSE TO DEFICIENCIES 11-13

The firm provided a response to deficiencies 11-13 (Item #60) on page 26 of the overall response summary. NuPathe states that section 6.9 of the new SOP QS-017, Design Control and Device Development, describes the process for how

(b) (4)

Section 6.9, Design Changes (820.30(j)), is found on page 13 of SOP QS-017, Rev 1. The procedure states (b) (4)

(b) (4)

Section 6.9 also discusses (b) (4)

The determination of need and appropriateness of (b) (4)

The response appears adequate.

The procedure states that SOP QS-002: (b) (4)

This document will be reviewed in the Manufacturing Section of this memo.

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.30(i).

Design History File, 820.30(j)

The firm describes the contents of the Design History File in SOP QS-003:

Design Control and Pharmaceutical Development, Section 4.12. It outlines all of

(b) (4)

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.30(j).

SECTION II: MANUFACTURING INFORMATION:

Quality System Procedures, 820.20(e)

The firm provided copies of all their quality control procedures relevant to the quality system and manufacturing. They provide a list of all of their quality system procedures.

This includes procedures for:

(b) (4)

There is no traditional "Quality Manual" included that summarizes all the quality policies and procedures taking place at the firm. However, the list (outline) of procedures was provided, and all of the necessary parts of the quality system seem to be included in that list.

Some basic issues with quality documentation were noted in this review. No procedures contained a scope to establish a limit of when and where procedures are to be applied.

DEFICIENCY 14

You provided documents including SOP QS-003, TM-0002, TM-0003, TM-0004, SOP QS-009, SOP QS-001, SOP QS-002, SOP QS-004, SOP 10-005, SOP QS-007, SOP QS-008, SOP QS-009, SOP QS-101, SOP QS-011, SOP QS-013, SOPQS-013, SOP 10-015, SOP QS0916, SOP 25-001, SOP QA-002, SOP QA-014, SOP QA-020 and SOP RA-001 in order to satisfy the requirements of 21 CFR 820. In these procedures, you describe the objective, responsibilities, procedure steps, and references related to each procedure. However, none of your procedures contain a scope, which should identify the limits as to when and where a procedure is to be applied. Please provide updated procedures that contain relevant scopes as to when and where the procedures are to be applied.

RESPONSE TO DEFICIENCY 14:

The firm provided a response to Deficiency 14 (Item 53) on page 22 of their overall response letter. NuPathe states that they have updated all the procedures relevant scope sections. Two procedures have been renamed – SOP 10-005 is now SOP QS-05, and SOP 25-001 is now SOP QA-001.

The response appears adequate.

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.20(e).

Production Flow

A production flow is provided in “device-info-amend-3-14-2011.pdf” that describes (b) (4) production areas involved in production of the E-Patch.

These areas are:



Use of Standards

The firm provided two standards for sampling procedures: ANSI/ASQ Z1.4 and ASQ Z1.9. Other standards were provided in the initial NDA submission, Section 3.2.R.4.2

The standards in Section 3.2.R.4.2 include

Table 1: Standards Used in the Development and Evaluation Process

Recognition List Number	Recognition Number	Standard	Title
018	5-40	(b) (4)	(b) (4)
020	13-8		
020	5-28		
020	9-46		

Purchasing Controls, 820.50

The firm provided SOP QS-012: Purchasing (revision .02) and SOP QS-016:

(b) (4)

SOP QS-012: (b) (4)

(b) (4)

(b) (4)

NOTE – (b) (4)

(b) (4)

(b) (4)

(b) (4)

NOTE - (b) (4)

(b) (4)

DEFICIENCY 15

You provided SOP QS-012: Purchasing (revision .02) in order to satisfy the requirements of 21 CFR 820.50, Purchasing Controls. In this SOP, you state that

(b) (4)

Reference is made to "Purchasing Policy 2010_2.0" in this procedure.

DEFICIENCY 16

You provided SOP QS-012: Purchasing (revision .02) in order to satisfy the requirements of 21 CFR 820.50, Purchasing Controls. In this SOP, you reference "Purchasing Policy 2010_2.0". However, this policy could not be found in your submission. Please provide this Policy, or the location where it may be found in your submission.

NOTE – *In the provided procedures, there is no discussion about* (b) (4)

SOP QS-016: External Auditing is a procedure that discusses how supplier audits are to occur. It details the responsibilities of (b) (4)

(b) (4)

RESPONSE TO DEFICIENCIES 15 and 16

The firm provided a response to deficiencies 15 and 16 (Item #62) on page 27 of the overall response summary. NuPathe has provided SOP GN-005 (Previously numbered SOP QS-012, which was previously named (b) (4)

SOP GN-005, Rev 00, is used for all (b) (4)

Section 6 of SOP QS-008, Rev 3, describes the situation above under (b) (4)

SOP QS-008 and SOP GN-005 still do not discuss potential differences in (b) (4)

NEW DEFICIENCY 1

You provided SOP GN-005, Rev 00, and SOP QS-008, Rev 3, in order to satisfy the requirements of 21 CFR 820.50, Purchasing Controls. In these procedures, you describe how (b) (4)

(b) (4)

Please provide a procedure which describes how (b) (4)

DEFICIENCY 17

You provided SOP QS-012: Purchasing (revision .02) and SOP QS-016: External Auditing in order to satisfy the requirements of 21 CFR 820.50, Purchasing Controls. In these procedures, you describe how purchases are made by (b) (4)

(b) (4)

RESPONSE TO DEFICIENCY 17

The firm provided a response to deficiency 17 (Item #63) on page 28 of the overall response summary. NuPathe has provided SOP GN-005 (Previously numbered SOP QS-012, which was previously named (b) (4)). NuPathe has also provided (b) (4)

SOP GN-005 explains (b) (4)

These procedures appear acceptable in relation to this deficiency, however there is still the concern regarding documenting risk. Typically, firms use a table of risk outlining the most critical types of suppliers based on risk to the function of the device, and those suppliers require some certification or higher audit frequency. Lower risk levels have lower levels of initial qualification or auditing frequency after that. NuPathe has not provided any such table or description that divides up suppliers by risk. See the above deficiency.

The response appears adequate.

The procedures provided by the firm have inadequately addressed the

requirements of 21 CFR 820.50.

Production and Process Controls, 820.70

The firm provides MS-009: NP101 Electrode Patch (500001) and controlled drawing 500001: Electrode Patch Assembly. The firm states that the assembly process is controlled by (b) (4).

The firm does not provided environmental or contamination control information for production of the E-Patch. However, given the processes described in assembly of the E-Patch and (b) (4) packaging, it seems that these are processes which should at have environmental controls. Of greatest concern are dust levels, required (b) (4) adhesives, etc.

DEFICIENCY 18

You provided the document, "device-info-amend-3-14-2011.pdf", section 2.7: Production and Process Controls, 820.70, as a summary discussing your production and process controls as required by 21 CFR 820.70. In this summary, you describe how assembly of the E-Patch is controlled. However, no environmental or contamination controls for manufacture of the E-Patch could be found. Please provide environmental and/or contamination control documentation for assembly of the E-Patch and (b) (4) packaging as required by 21 CFR 820.70(c), Environmental Control, and 21 CFR 820.70(e), Contamination Control.

RESPONSE TO DEFICIENCY 18

The firm provided a response to Deficiency 18 (Item #66) on page 29 of the overall response summary. NuPathe uses (b) (4). This appears appropriate as the environmental controls are (b) (4).

The response appears adequate

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.70.

Inspection, Measuring, and Test Equipment, 820.72

No general procedure for maintaining calibration files and having primary responsibilities for making sure that calibrations are accomplished at specific intervals is provided.

The firm provided four procedures describing how inspection, measuring and test equipment is routinely calibrated, inspected, checked, and maintained.

- a) SOP 75-002: Operation, Maintenance and Calibration of the Electrode Capacity Tester
- b) SOP 75-003: Operation, Maintenance and Calibration of the Electrode Card/Patch Tester
- c) SOP 75-007: Operation, Maintenance and Calibration of the Electrode Patch Connectivity Tester
- d) SOP 75-009: Operation and Maintenance of the (b) (4) Battery Tester

a) SOP 75-002 – This procedure discusses (b) (4)
[Redacted]

b) SOP 75-003 – This procedure discusses (b) (4)
[Redacted]

c) SOP 75-007 – This procedure discusses (b) (4)
[Redacted]

d) SOP 75-009 – This procedure describes operation and maintainance of the (b) (4) Battery Tester, which tests (b) (4). No information regarding calibration could be found.

DEFICIENCY 19

You provided SOP 75-009: Operation and Maintenance of the (b) (4) Battery Tester to satisfy the requirements of 21 CFR 820.72, Inspection, Measuring, and Test Equipment. In this procedure, you describe how to operate the Battery Tester. However, the procedure does not describe the need to calibrate the instrument, and if it is required, how often, by whom, and where the calibration record will be stored. Please provide a procedure for the (b) (4) Battery Tester that addresses the requirements for calibration of 21 CFR 820.72(b), Calibration.

RESPONSE TO DEFICIENCY 19

The firm provided a response to Deficiency 19 (Item #64) on page 28 of the overall response summary. NuPathe has renamed SOP 75-009 to SOP CM-009

(b) (4)

The response appears adequate

DEFICIENCY 20

You provided four procedures, SOP 75-002, SOP 75-003, SOP 75-007, and SOP 75-009. In these procedures, you describe maintenance, operation, and calibration of four different pieces of test equipment. However, it is not clear if these procedures describe all of your inspection, measuring, and test equipment, or if they represent a sample. Please provide a list of other inspection, measuring, and test equipment used for the manufacture of the E-Patch and (b) (4) Packaging, and a procedure that describes how your calibration records are kept for your equipment.

RESPONSE TO DEFICIENCY 20

The firm provided a response to Deficiency 20 (Item #65) on page 28 of the overall response summary. NuPathe states that all (b) (4)

NuPathe states that in general (b) (4)

Section 3.2.R.4.4.5.5 describes all (b) (4)

The response appears adequate.

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.72.

Process Validation, 820.75

The firm provides a list of processes to validate in the “device-info-amend-3-14-2011.pdf” document, section 2.7 Process Validation, 820.75. Those processes

are – [REDACTED] (b) (4)

I am reviewing the Electrode Patch Assembly and [REDACTED] (b) (4) packaging processes, as those are the finished devices.

Section 2.7.4 discusses the Electrode Patch (E-Patch) assembly process. The critical parameters of the E-Patch assembly process are: [REDACTED] (b) (4)

Section 2.7.5 discusses the [REDACTED] (b) (4) Packaging process. Critical parameters are identified to be – [REDACTED] (b) (4)

[REDACTED] (b) (4)

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.75.

Process Validation, 820.75(a)

The firm provides plans for the validation of the following

A. Electrode

DEFICIENCY 21

You provide a process validation plan in "device-info-amend-3-14-2011.pdf," section 2.8 Process Validation, 820.75(a). In this plan, you describe your Electrode testing validations to be conducted from [REDACTED] (b) (4)

(b) (4)
Please provide a process validation procedure for your Electrode testing validations that include (b) (4) for your (b) (4) plan.

Acceptance criteria are provided for the electrode as – (b) (4)

DEFICIENCY 22

You provide a process validation plan in “device-info-amend-3-14-2011.pdf,” section 2.8 Process Validation, 820.75(a). In this plan, you describe your acceptance criteria to be (b) (4). However, these criteria appear to be subjective, rather than objective and measurable. Please provide an updated Electrode process validation plan and process validation procedure that provides objective and measurable acceptance criteria.

B. E-Patch

(b) (4)

DEFICIENCY 23

You provide a process validation plan in “device-info-amend-3-14-2011.pdf,” section 2.8 Process Validation, 820.75(a). In this plan, you describe how the E-Patch process will be validated. However, you have not provided a procedure for this validation. Please provide a validation procedure for your E-Patch process. As a reminder, process validations must be completed prior to the pre-approval inspection.

C. (b) (4) Packaging

(b) (4)

DEFICIENCY 24

You provide a process validation plan in "device-info-amend-3-14-2011.pdf," section 2.8 Process Validation, 820.75(a). In this plan, you describe how the (b) (4) Packaging will be validated with (b) (4)

However, no statistical rationale could be found in your plan for why (b) (4)

Please provide an updated process validation plan and a process validation procedure for (b) (4) Packaging that contains a statistical rationale for your (b) (4) plan.

DEFICIENCY 25

You provide a process validation plan in "device-info-amend-3-14-2011.pdf," section 2.8 Process Validation, 820.75(a). In this plan, you describe that your packaging will be validated. However, no acceptance criteria could be found in relationship to this validation. Please provide an updated process validation plan and a process validation procedure for (b) (4) Packaging that contains objective and measurable acceptance criteria.

RESPONSE TO DEFICIENCIES 21-25

The firm provided a response to Deficiencies 21-25 (Item #67), on page 30 of the overall response summary. NuPathe states the following:

1. (b) (4)
Validation is discussed further in Section 3.2.R.4.4.7. (Section 3.2.R.4.4.7 describes the Master Validation Plan, which follows the (b) (4) Quality Management Systems – Process Validation Guidance for determining information required in each validation protocol)
2. Electrode validation batches will be evaluated per NuPathe specification RS-002 (RS-002, Electrode (300050), Rev 1, describes test specifications and acceptance requirements for (b) (4). Validation tests are provided in the appendices and appear complete).
3. E-Patch validation is discussed in Section 3.2.R.4.4.7.1.4. (This section states that validation is (b) (4)
The validation will be provide documented

DEFICIENCY 26

You provided "device-info-amend-3-14-2011.pdf," Section 5.1 Receiving Acceptance Activities to describe receiving acceptance activities at (b) (4) and at NuPathe's facilities. In your description, you state that (b) (4). However, you have not provided sufficient documentation of (b) (4) are being performed. Please provide either documentation of (b) (4)

RESPONSE TO DEFICIENCY 26

The firm provided a response to Deficiency 26, (Item #68), on page 31 of the overall response summary. NuPathe states that (b) (4)

Section 3.2.P.5.1 includes a (b) (4)

SOP QA-014 defines acceptance procedures as (b) (4)

The response appears adequate

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.80(b).

Final Acceptance Activities, 820.80(d)

DEFICIENCY 27

You provided "device-info-amend-3-14-2011.pdf," Section 5.2 Final Acceptance Activities, 820.80(d) to describe [REDACTED] (b) (4)

[REDACTED] In your description, you state that [REDACTED] (b) (4).
[REDACTED] However, you have not provided sufficient documentation of [REDACTED] (b) (4).

RESPONSE TO DEFICIENCY 27

The firm provided a response to Deficiency 27, (Item #69), on page 31 of the overall response summary. The response is identical to that for Item #68. NuPathe states that [REDACTED] (b) (4)

Section 3.2.P.5.1 includes a [REDACTED] (b) (4)

SOP QA-014 defines [REDACTED] (b) (4)

The response appears adequate.

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.80(d).

Nonconforming Products, 820.90

The firm provided the following procedures that relate to nonconforming product.

1. SOP QS-011: Non-Conformance and CAPA Management
2. SOP QA-002: Processing Marketed Product Related Complaints and Inquiries
3. SOP QA-014: Release of Batch Record Processed Material

SOP QS-011 – [REDACTED] (b) (4)

[Redacted] (b) (4)

Section 3.2: Product or Material Non-Conformance describes definitions for the various types of nonconformances.

Section 4.0: Identification and Notification of Non-Conformances and Deviations

– [Redacted] (b) (4)

Section 5.0-5.3 describes how [Redacted] (b) (4)

[Redacted]

SOP QA-002 – This procedure governs [Redacted] (b) (4)

[Redacted]

SOP QA-014 – This procedure describes the [Redacted] (b) (4)

[Redacted]

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.90.

Corrective and Preventive Action (CAPA), 820.100

The firm has provided SOP QS-011: Non-Conformance and CAPA Management to satisfy the requirements of 21 CFR 820.100. This procedure was reviewed here in the previous section (Nonconforming Product).

SOP QS-011 addresses [Redacted] (b) (4)

DEFICIENCY 28

You provided SOP-QS-011: Non-Conformance and CAPA Management to satisfy the requirements of 21 CFR 820.100. In this procedure, you describe how

(b) (4)

Please provide an updated CAPA procedure that describes how a determination to conduct a corrective or preventive action is conducted.

DEFICIENCY 29

You provided SOP-QS-011: Non-Conformance and CAPA Management to satisfy the requirements of 21 CFR 820.100. In this procedure, you describe

(b) (4)

Please provide a CAPA procedure that addresses all the requirements of 21 CFR 820.100, Corrective and Preventive Action (CAPA).

RESPONSE TO DEFICIENCIES 28 and 29

The firm provided a response to Deficiencies 28 and 29 (Item #61) on page 26 of the overall response summary. NuPathe has *(b) (4)*

(b) (4)

Sections 8.4 and 8.5 of SOP QS-011 describe using *(b) (4)*

(b) (4)

Section 5.1 on page 4 of SOP QS-022, Rev 00, states that [REDACTED] (b) (4)

Section 5.6 on page 5 of SOP QS-022 describes [REDACTED] (b) (4)

Section 7.2 describes the [REDACTED] (b) (4)

Section 8.4 outlines the [REDACTED] (b) (4)

The response appears adequate.

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.100.

Complaint Files, 820.198

The firm is reporting under adverse drug reporting requirements of 21 CFR 314.80, which is the appropriate adverse reporting procedure for drugs.

DEFICIENCY 30

You provide SOP QA-002: Processing Marketed Product Related Complaints and Inquiries, to satisfy the requirements of 21 CFR 820.198, Complaint Files. In this procedure, you cite SOP RA-013 as the procedure used by [REDACTED] (b) (4)

[REDACTED]

DEFICIENCY 31

You provide SOP QA-002: Processing Marketed Product Related Complaints and Inquiries, to satisfy the requirements of 21 CFR 820.198, Complaint Files. In this procedure, [REDACTED] (b) (4)

Please provide a complaint file procedure that satisfies these requirements of 21 CFR 820.198, Complaint Files.

RESPONSE TO DEFICIENCIES 30-31

The firm provided a response to Deficiencies 30-31 (Item #54) on page 22 of the overall response summary. NuPathe states that SOP QA-002 (Processing Marketed Product Related Complaints and Inquiries) and SOP RA-013 (Adverse Drug Experience Reporting for Marketed Products) have been updated to satisfy the requirements of 21 CFR 820.198 and 21 CFR 803.

SOP QA-002, Rev 01, states that [REDACTED] (b) (4)

SOP RA-013, Rev 04, describes how to [REDACTED] (b) (4)

[REDACTED] Reportability appears to be following CDER regulations. This appears appropriate, but CDER should review for completeness.

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.198.

SEE LIST OF DEFICIENCIES BELOW

You provided SOP GN-005, Rev 00, and SOP QS-008, Rev 3, in order to satisfy the requirements of 21 CFR 820.50, Purchasing Controls. In these procedures, you describe how [REDACTED] (b) (4)

[Redacted] (b) (4)

However, it is not clear how product or service risk, for example, a [Redacted] (b) (4)

Please provide a procedure which describes how [Redacted] (b) (4)

You provided a response to deficiencies regarding Process Validation, 820.75(a). In the response, you state that [Redacted] (b) (4) packaging [Redacted] (b) (4)

Please provide a validation protocol for the [Redacted] (b) (4) packaging process.


LCDR Elijah M. Weisberg

Prepared: **EWeisberg: 11/29/2012**
Reviewed:
Lead Reviewer: **EWeisberg: 11/29/2012**
Co- Reviewer: **N/A**

Final: **FMLast: date**

cc:
WO66-1521 ODE/POS
WO66-3521 OC/FPB/PMA Program Coordinator
WO66-xxxx **(Insert last name of ODE/OIVD Lead Reviewer to Copy into IMAGE.)**
WO66-xxxx **(Insert your last name as DOE/OIVD Lead Compliance Reviewer.)**
WO66-xxxx **(Insert the last name as DOE/OIVD Compliance Co-Reviewer.)**

OC Doc. No.: **CON1216871**
NDA #**202278**

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

/s/

TESHARA G BOUIE

12/07/2012

Checking in DARRTS on behalf of Elijah Weisberg, CDRH OC.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling, Packaging, and Usability Study Review

Date: November 27, 2012

Reviewer: Julie Neshiewat, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Zecuity (Sumatriptan) Iontophoretic Transdermal
System
6.5 mg over 4 hours

Application Type/Number: NDA 202278

Applicant/sponsor: NuPathe

OSE RCM #: 2012-1597

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed labels, labeling, packaging, and usability study results for Zecuity (Sumatriptan) Iontophoretic Transdermal System, NDA 202278, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

This is a 505(b)(2) application. The Applicant submitted the original application on October 29, 2010. The Division of Neurology Products (DNP) issued a Complete Response (CR) letter for this application secondary to Chemistry, Manufacturing, and Controls (CMC) and device deficiencies on August 29, 2011. At the End of Review Meeting on November 9, 2011, the Agency stated that the current design does not ensure safe use of the product. The Center for Devices and Radiological Health (CDRH) commented that the usability study results submitted on July 11, 2011 confirmed that a fraction of users had difficulty assembling the device. The usability study results submitted on July 11, 2011 were not reviewed by the Division of Medication Error Prevention and Analysis (DMEPA). At the Type A CMC Meeting on March 7, 2012, the Applicant provided information regarding their new product design. The Applicant stated that the burn issues identified during the first review cycle have been resolved with the use of a pad detection system. The Applicant resubmitted this application on July 17, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the August 17, 2012 proprietary name submission.

- Active Ingredient: Sumatriptan
- Indication of Use: Acute treatment of migraine attacks, with or without aura, in adults
- Route of Administration: Transdermal (Topical)
- Dosage Form: Iontophoretic Transdermal System
- Strength: 6.5 mg over 4 hours
- Dose and Frequency: Apply one patch; maximum recommended dose is two patches in 24 hours, separated by at least 2 hours
- How Supplied: Cartons of 6 patches
- Storage: Room temperature
- Container Closure System: Consists of two reservoir cards, the Drug Reservoir Card (DRC) and the Salt Reservoir Card (SRC). Each reservoir card is manufactured by (b) (4)

2 METHODS AND MATERIALS REVIEWED

Although Sumatriptan is currently marketed, there are no iontophoretic transdermal systems currently marketed that could inform our review. Therefore, DMEPA did not search the FDA Adverse Event Reporting System (FAERS) database for medication error reports. We reviewed the Sumatriptan Iontophoretic Transdermal System labels, labeling, packaging, and usability study results submitted by the Applicant.

2.1 LABELS, LABELING, AND USABILITY STUDY

Using the principals of human factors and Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Patch Label submitted on July 17, 2012 (Appendix A)
- Container Label submitted on July 17, 2012 (Appendix B)
- Carton Labeling submitted on July 17, 2012 (Appendix C)
- Instructions for Use submitted on July 17, 2012 (Appendix D)
- Patient Instructional Video submitted on July 17, 2012 (No image)
- Risk Analysis submitted on July 17, 2012 (No image)
- Usability Study NP101-027 Results submitted on July 17, 2012 (Study was conducted on June 7, 2012)
- Insert Labeling submitted October 16, 2012 (No image)

3 MEDICATION ERROR RISK ASSESSMENT

The sections below discuss the results of our review of Usability Study NP101-027 and our label, labeling, and packaging risk assessment.

3.1 USABILITY STUDY NP101-027

3.1.1 Study Design

This study was a single center, open label study assessing a single application of the proposed product. Participating subjects either had a history of migraine or were health care professionals. Subjects were divided into three groups:

Group 1: Subjects with a history of migraine not trained to use the proposed product
- Received the IFU, patient labeling, and patient video at screening to take home
- Subjects reported to the testing facility when he/she experienced a migraine headache to assemble and apply the patch

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Group 2: Health care professionals not trained to use the proposed product
- Given the option to read the IFU and/or watch the patient video before assembling and applying the patch

Group 3: Subjects with a history of migraine trained to use the proposed product
- Received training that mimicked instructions from their health care provider including assembling and applying a patch under the guidance of the trainer
- Subjects reported to the testing facility when he/she experienced a migraine headache to assemble and apply the patch

A minimum of 16 subjects (8 in Group 2 and 8 in Group 3) participated in a pre-summative usability test and 48 subjects (16 in each of the three groups) participated in the formal summative study. Subjects were 18 years to 65 years of age. Based on migraine incidence rates, approximately 80% of recruited subjects were female and 20% male.

The purpose of the pre-summative test was to identify any unforeseen usability and/or methodological issues associated with the patch or instructional materials that might jeopardize the success of the summative usability test.

There were no user errors, close calls, or operational difficulties observed in the pre-summative testing. Since the results of the pre-summative testing showed 100% success of assembling, applying, and activating the patch correctly, there were no modifications made to the patient instructions for use, patient labeling, or patient video prior to proceeding to the formal summative testing.

The purpose of the formal summative study was to validate subjects could correctly assemble and correctly apply the proposed product. The clarity of the instructional materials and the ease of use were also assessed in the study.

3.1.2 Study Results

The formal summative testing results indicated that 100% of the patches were assembled, applied, and activated successfully with no user errors, one close call, and no operational difficulties observed. The close call describes a patient who took the cardboard apart and removed the patch with the foil backing attached. When she attempted to apply the patch with the foil, she realized the mistake and corrected it. Across all three groups, the mean score for ease of assembly was 6.1 and the mean score for ease of application/activation was 6.8 when rated on a scale of 1 to 7 with 1 being difficult and 7 being easy.

Although the usability study indicates that 100% of the subjects could assemble, apply, and simulate activation of the patch successfully, we are concerned that the usability study did not evaluate all use aspects of the product. We note that the Applicant's risk analysis identified hazards that were not evaluated in the usability study. For example, the risk analysis states that "Multiple patches activated in less than 2 hours cause increased drug delivery," but the usability study did not evaluate the subject's understanding of when additional patches can be applied. The insert labeling states that "(b) (4)". It is not intuitive for the patient to know that a second patch can be applied 2 hours after the first patch is applied. After discussing this issue with the review team, the review team

clarified that the Applicant does not have sufficient evidence to support a second dose, and therefore redosing within 24 hours will be removed from the insert labeling. We also note that the usability study did not evaluate removal and disposal of the patch; however, the removal and disposal of the patch is similar to other marketed transdermal products in which the patch should be folded so that the adhesive side sticks to itself.

3.2 LABEL AND LABELING DEFICIENCIES NOTED

The strength statement on the labels and labeling should be revised to indicate the amount of drug delivered over a period of time for clarity. We note that there is important information found in the Applicant's risk analysis that was not included in the IFU. For example, the risk analysis states that "Applying patch to same site less than 72 hours after erythema is resolved could result in increased drug delivery," but this information is not found in the IFU. Information added to the IFU should also be added to the patient instructional video for consistency. The usability study indicates that subjects could assemble, apply, and simulate activation of the patch safely. There is still concern for accidental exposure with the current design of the product. If a patch is removed before the 4 hours, it takes one hour for the patch to deactivate. During that one hour period to deactivate, if the patch was not properly disposed, there is potential that a child may apply the patch and receive medication. The review team was notified of this potential issue at a team meeting.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

- A. Comments to the Division
 1. Insert Labeling
 - a. General Comment: The use of all uppercase letters for the proposed proprietary name, ZECUITY, can remain in the title of the insert labeling. However, we recommend that the proposed proprietary name, ZECUITY, in all upper case be revised to title case, Zecuity, for improved readability throughout the rest of the insert labeling.
 - b. Section 2 Dosage and Administration
 - i. We recommend that a statement similar to "The patch should not be cut" be included to prevent manipulation of the product.
 - ii. The abbreviation LED is utilized. We recommend that the abbreviation be defined the first time it is mentioned for clarity.
 - iii. It is unclear if a patient can utilize other sumatriptan products with the proposed product. If the Applicant provided data to support use of the proposed product with other sumatriptan products, we recommend that these specific instructions be included.

- c. Section 16 How Supplied/Storage and Handling: We recommend that the statement (b) (4) be revised to read ‘Store at room temperature 20°C to 25°C (68 °F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F)’. Removing the hyphens and replacing with ‘to’ will help to improve readability and increase clarity of the information presented.
- d. Section 17 Patient Counseling Information: We recommend that a statement similar to “Inform patients that the safety of more than six Zecuity applications in one month has not been evaluated” be included under Section 17.9 as the last paragraph, since this is important information regarding the safe use of the product.
- e. Patient Information
 - i. We recommend that a statement similar to “The transdermal system should not be cut” be included to prevent manipulation of the product. This statement can appear as the fourth bullet point under the section “How should I use Zecuity?”
 - ii. We recommend that a statement similar to “Zecuity is a single-use patch” be included to prevent re-use of the product. This statement can appear as the fifth bullet point under the section “How should I use Zecuity?”

B. Comments to the Applicant

1. Patch Label: Revise “(b) (4)” to read “6.5 mg delivered over 4 hours” for clarity. In addition, ensure that there is a space between the number and the unit for improved readability. For example, revise “6.5mg” to read “6.5 mg.”
2. Container Label
 - a. See Comment B.1. In addition, increase the font size of the strength statement “6.5 mg delivered over 4 hours.”
 - b. Remove the graphic appearing to the left of the proposed proprietary name, Zecuity. This graphic detracts from other important information on the label and could be misinterpreted as an additional letter in the proprietary name.
 - c. The font for the dosage form “Iontophoretic Transdermal System” should match the font utilized for the presentation of the active ingredient “Sumatriptan” in size, typography, and color.
 - d. Add the statement “For transdermal use only” on the principal display panel per 21 CFR 201.100(b)(3).
 - e. Debold the “Rx Only” statement on the back panel since it is overly prominent.

- f. Negative warnings, such as “do not do that” can be misread as an affirmative warning “do this.”² The negative warning should be changed to an affirmative to prevent misinterpretation. Therefore, we request you revise the statement [REDACTED] (b) (4) to read “Single-use only. Discard after initial use.”
 - g. Revise the statement [REDACTED] (b) (4) to read “Store Zecuity at room temperature 20°C to 25°C (68 °F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F)”. Removing the hyphens and replacing with ‘to’ will help to improve readability and increase clarity of the information presented.
 - h. Revise statements in all upper case to title case. For example, revise “BEFORE OPENING POUCH, READ INSTRUCTIONS FOR USE” to “Before Opening Pouch, Read Instructions for Use” for improved readability.
 - i. Decrease the size of the NuPathe logo since it detracts from other important information.
 - j. Revise the statement [REDACTED] (b) (4),” to read “Press firmly while tracing arrow 3 times around” for clarity.
3. Carton Labeling
- a. See Comments B.2.a. to B.2.i.
 - b. The Quick Response (QR) Code that appears on the principal display panel should be relocated to a side or back panel, away from the barcode. The size of the QR Code should also be minimized so that it does not detract from other important information on the panel.
 - c. Decrease the font size of the net quantity statement [REDACTED] (b) (4),” since it is overly prominent.
4. Instructions for Use
- a. The figures utilized in the IFU should be revised to include a more representative picture of the actual carton labeling and patch for clarity.
 - b. Add a statement similar to “Skin at the application site should be free of irritation for 72 hours prior to applying Zecuity” under the “Preparation” section, since this information is important and should be captured in the IFU.
 - c. Add a statement similar to “Zecuity contains lithium-manganese dioxide batteries. Dispose in accordance with state and local

² Institute for Safe Medication Practices (ISMP). August 12, 2010. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Medication Safety Alert, 15(16).

regulations.” under the “Removal & Disposal” section, since this information is important and should be captured in the IFU.

- d. Add statements similar to “Zecuity is a single-use patch. The transdermal system should not be cut.” under the “Important” section, since this information is important and should be captured in the IFU.
 - e. Add a statement similar to “Do no undergo a Magnetic Resonance Imaging (MRI) while wearing Zecuity.” under the “Wearing Zecuity” section, since this information is important and should be captured in the IFU.
 - f. Add a statement similar to “There may be residual gel left in the reservoirs after the patch is peeled back from the liner” under Step 3 to notify patients that they may see residual gel left in the reservoirs.
5. Patient Instructional Video: For consistency, the information added to the IFU should also be added to the patient instructional video. Additionally, the sequence of information in the video should also correspond to the sequence of information found in the IFU.

If you have further questions or need clarifications, please contact Laurie Kelley, project manager, at 301-796-5068.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JULIE V NESHIEWAT
11/27/2012

IRENE Z CHAN
11/27/2012

CAROL A HOLQUIST
11/27/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: November 26, 2012

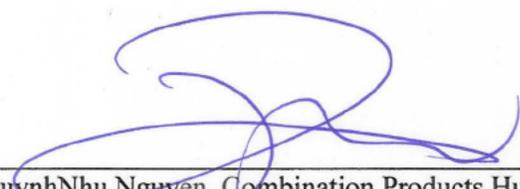
FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID

CC: Molly Story, Human Factors and Accessible Medical Technology Specialist, DAGID

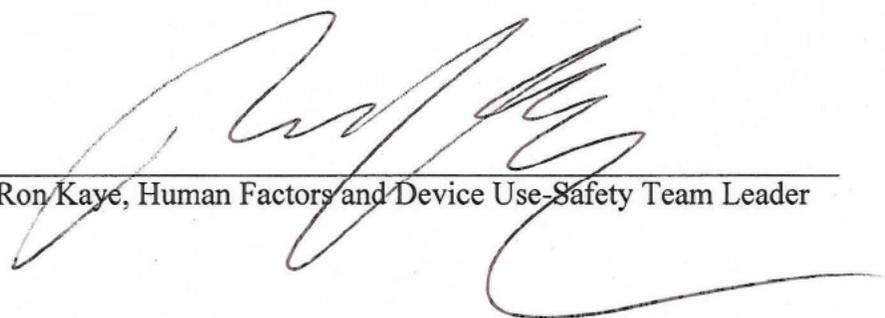
TO: Lana Chen, Regulatory Project Manager, CDER/OND/ODEI/DNP

SUBJECT: NDA 202278
Drug: Zelrix (sumatriptan, migraine)
Device: Patch
CDRH CTS Tracking: ICC1200147, CON1216691



QuynhNhu Nguyen, Combination Products Human Factors Specialist

11/26/2012
Date



Ron Kaye, Human Factors and Device Use-Safety Team Leader

11/26/2012
Date

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CDRH Human Factors Review

Overview and Recommendations

The Division of Neurology Products, Office of Drug Evaluation I, Office of New Drugs, Center for Drugs Evaluation and Research requested a Human Factors consultative review of the NDA 202278 submitted by NuPathe for Zecuity medication patch.

The Agency previously requested that a comprehensive risk analysis to identify use related and medication error risks, and to conduct a usability study to demonstrate that the NP101 patch could be used without producing patterns of failures that could result in a negative clinical impact to patients. As a result, the Sponsor completed a usability study (NP101-021) which resulted in a number of close calls and/or operational difficulties noted during assembly. The Agency continued to have concerns of the potential consequences of misapplication or absent patch medication pads and the potential risk of patch being misassembled and misaligned that could result in significant safety consequences (skin burns). Subsequently, NP101 has undergone a device enhancement i.e. adding a new pad detection system (PDS) safety feature to address the misapplication concern. This modification ensures that in the event a patch is misassembled or medication pad(s) are absent, NP101 will not turn on (enter active dosing mode). In addition, the modified enclosed (b) (4) packaging design. The enclosed (b) (4)

This review covers the study report titled “An Open-Label, Randomized, Single Center, Single Application Usability Study of NP101 in Adult Subjects” (NP101-027) and the risk (sequence 31, 3.2.R REH-DHF-NP101-296. The risk analysis was not clear how the sponsor mitigated the risk of the user taking both the oral medication and the medication patch. In addition, this validation study was conducted with 16 participants in a small scale pilot/pre-validation test, and 48 participants in the actual validation test. All participants were asked to perform a simulated patch application. The Sponsor reported that 100% of test participants were able to assemble, apply, and activate the patch successfully with no close calls or operational difficulties were observed in the pre-validation study, and 0 (0.0%) use errors, 1 (2.1%) close call (Group 3), and 0 (0.0%) operational difficulties observed in the validation study. Subjective data were also collected via interviews and provided in appendices I and J of the study report. The subjective data indicated some concerns from the user perspective; however, the Sponsor did not address those concerns in the report. The reviewer identified two deficiencies and requested the Project Manager to communicate the deficiencies to the Sponsor. The Sponsor provided a response on 11/26/2012.

Reviewer's Recommendations

While the reviewer finds the Sponsor's response acceptable from a usability's perspective, the reviewer defers to the clinical team to determine whether there is significant clinical harm when a patient experiences delayed therapy when they are prescribed to this product. The reviewer discussed this concern with the medical officer on the team, and it is the reviewer's understanding that there is no significant clinical harm associated with delayed therapy with the exception that the patient continues to experience migraine.

Regarding the potential risk of improper dosing/administration exists when a patient takes both the orally prescribed medication and the patches concurrently. The reviewer defers to the clinical team to evaluate whether there is any significant clinical harm when the oral pills and the patches are used concurrently. If the oral pills and the patches should not be used concurrently, then the reviewer recommends that the product IFU and labeling and physician's information clearly states that the oral pills and the patches should not be used concurrently. The reviewer discussed this concern with the medical officer on the team, and both agreed that including information in the IFU/labeling and physician's information would reduce the potential risk of improper dosing/administration of different migraine products at the same time.

APPEARS THIS WAY ON ORIGINAL

CDRH Human Factors Review

Combination Product Device Information

Submission Number: NDA 202278
Applicant: NuPathe
Drug Constituent: Zecuity
Device Constituent: medication patch
Intended Use: migraine

CDRH Human Factors Involvement History

Date	Involvements
8/14/2012	CDRH HF team was requested to provide a consultative review
11/26/2012	CDRH HF team provided review comments/deficiencies to CDER

Summary of Review Materials

This review covers the study report titled “An Open-Label, Randomized, Single Center, Single Application Usability Study of NP101 in Adult Subjects” (NP101-027). In addition to the final validation study report, NP101-027, the Sponsor submitted a risk analysis. The risk analysis was not clear how the sponsor mitigated the risk of the user taking both the oral medication and the medication patch.

This study was conducted with 16 participants in a small scale pilot/pre-validation test, and 48 participants in the actual validation test. Since the pilot/pre-validation test did not show any major issues, the sponsor considered the data obtained from the 16 participants as part of the validation test. The breakdown of the test participants is as follows:

- 40 participants with migraine (16 untrained and 24 trained)
- 24 healthcare providers

The untrained participants received the patch instructions for use, patient labeling, and patient video at screening to take home with them. The trained participants received training from a trainer. Using the same materials, the trainer reviewed each of the “Application Instruction” steps while using a patch to demonstrate each of the steps. Each subject was asked if he/she had any questions. Each subject was asked if he/she understood how to assemble and apply the patch. The trainer could repeat the instructions if the subject indicated they did not understand. Subjects were provided the patch instructions for use, patient labeling, and patient video to take home with them. All participants then reported to the testing facility within approximately 4 hours of the onset of the migraine.

All participants were asked to perform a simulated patch application, which included the following tasks:

- Assemble the patch, and
- Apply the patch to an approved patch application site, and
- Simulate activating the patch but not depressing the button.

The Sponsor reported that 100% of test participants were able to assemble, apply, and activate the patch successfully with No close calls or operational difficulties were observed in the pre-validation study, and 0 (0.0%) use errors, 1 (2.1%) close call (Group 3), and 0 (0.0%) operational difficulties observed in the validation study.

Subjective data were also collected via interviews and provided in appendices I and J of the study report. The study participants were asked for their feedback on the video and instructions for use. They were also asked to respond to the following questions:

- whether they believe that they made any mistakes (task failures)
- were there any times when they come close to making a mistake but then avoid it (close call)
- did they experience any significant difficulties assembling and applying the patch (operational difficulties)
- is there anything about the patch that could cause someone to make mistakes that could lead to problems

The subjective response from test participants was grouped in three areas:

1. the strength required to pull the foil out of the packet might be an issue for older patients, or patients with manual dexterity issues i.e. arthritis
2. the steps could be performed out of sequence,
3. ensuring that the patches fully transfer to the electrodes

The Sponsor did not provide analysis so of the subjective data collected especially with the manual dexterity and strength required to pull the foil, which could represent delayed therapy. The Sponsor should be asked to address this concern.

The following provides the deficiencies issued to the Sponsor and the reviewer's evaluation of the Sponsor's response to those deficiencies.

Deficiencies

- I. You reported that 100% of test participants were able to assemble, apply, and activate the patch successfully with no close calls or operational difficulties were observed in the pre-validation study, and no use errors, 1 close call, and 0 operational difficulties observed in the validation study. However, the subjective data collected from test participants indicated that there were numerous close calls and operational difficulties based on your questions about come close to making mistake, and experience significant difficulty respectively. The following provided a summary of those concerns:

1. the strength required to pull the foil out of the packet might be an issue for older patients, or patients with manual dexterity issues i.e. arthritis
2. the steps could be performed out of sequence,
3. ensuring that the patches fully transfer to the electrodes

You did not provide analysis of the subjective data collected especially with the manual dexterity and strength required to pull the foil, which could represent delayed therapy, and the associated clinical impact. Please discuss how you have you believe the current design including Instructions for Use (IFU) and labeling have adequate mitigations to addressed the subjective concerns raised in the Study.

- II. You submitted a risk analysis for the proposed product. The risk analysis was not clear how you mitigated the risk of the user taking both the oral medication and the medication patch at the same time, which could lead to overdosing. Please provide a clarification.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>.

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>

Evaluation of Sponsor's Response to Deficiency I:

The Sponsor stated that despite the participant's perception on their ability to perform the task, the participants made no error, one close call, and no operational difficulties.

- With respect to the concern about the ability of a migraine patient to remove the foil, of the 10 subjects reported a medical condition that could be associated with a potential dexterity or strength impairment, only one subject indicated that their medical condition may have impacted their ability to remove the foil. However, this subject was able successfully remove the foil and assemble the product.
- With respect to the concern about the steps could be performed out of sequence, the device has an LED that provides a feedback to the user. If the device is not properly prepared, the LED will not turn on, or it will initially blink and then turn off and the IFU specified that the patch should be removed from skin.
- With respect to the concern about ensuring that the patches fully transfer to the electrodes, the product is designed such that the pads are aligned directly over the electrodes during product assembly. The IFU instruct patient to verify the pads are properly assembled.

Evaluation of Sponsor's Response to Deficiency II:

The Sponsor reported that during clinical study NP101-009, approximately 7,655 patches were applied with no reported instances of administration of another sumatriptan within two hours of patch application, indicating the probability of occurrence is low. In the event that simultaneous administration of sumatriptan did occur, the potential clinical severity is also low.

Device Description

NP101 is an iontophoretic transdermal patch with anode and cathode reservoir pads, when activated by depressing the button in the center of the dome, delivers ~ 6.5 mg of sumatriptan, using a low electrical current to produce a (b) (4)

(b) (4). The patch is a disposable, single-use device. Subjects in this study were advised to simulate pressing the button to activate the patch.

The drug reservoir pad (anode) formulation for all patches was:

- (b) (4) grams of sumatriptan formulation (b) (4) polyamine formulation with (b) (4) sumatriptan succinate containing 86 mg of sumatriptan [(b) (4) mg of sumatriptan succinate])
- The salt reservoir pad (cathode) formulation for all patches was:
 - (b) (4) grams salt formulation containing (b) (4) Hydroxypropylcellulose (HPC) with
 - (b) (4) sodium chloride (NaCl)
 -

Instructions for Use



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

/s/

LANA Y CHEN

11/27/2012

Placed in DARRTS for CDRH HF

MEMORANDUM

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

DATE: October 12, 2012

TO:  nch
(b) (4)

Director, Investigations Branch
Kansas District Office
11630 W. 80th St.
Lenexa, KS 66214

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2013, **CDER High Priority User Fee NDA, Pre-Approval
Data Validation Inspection**, Bioresearch Monitoring,
Human Drugs, CP 7348.001

RE: NDA 202-278
DRUG: Zecuity™ (sumatriptan iontophoretic
transdermal system) NP101, 6.5 mg
SPONSOR: NuPathe Inc.
Conshohocken, PA

This memo requests that you arrange for inspection of the clinical and analytical portions of the following bioequivalence studies. **A DBGLPC scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGLPC point of contact (POC) upon receipt of this assignment to arrange scheduling of the analytical inspection. Following identification of the FDA investigator, background materials will be forwarded directly. Please contact the POC for background materials. Please complete the inspection prior to December 02, 2012.**

Do not identify the application, the studies to be inspected, drug names, or the study investigator prior to the start of the inspection. The information will be provided to the site at the

inspection opening meeting. Please note that this inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, and not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of the completed sections A & B of this memo to Dr. Sam Haidar, and the DBGLPC POC listed at the end of this memo.

Study Number: NP101-023

Study Title: "A phase I, single center, open-label, randomized, single-dose, three-way crossover study to compare the pharmacokinetics and bioequivalence of two NP101 (Sumatriptan Iontophoretic Transdermal Patch) treatments with an oral formulation of Imitrex® in healthy volunteers"

Study Number: NP101-026

Study Title: "A phase I, single center, open-label, randomized, single-dose, two-way, crossover study to compare the pharmacokinetics and bioequivalence of two NP101 (sumatriptan iontophoretic transdermal system) patches and validation testing of the NP101 Pad Detection System"

Clinical Site: PRACS Institute
(Cetero Research)
400 Fountain Lakes Boulevard
St. Charles, MO 63301
TEL: 636-757-7108
FAX: 636-723-5888

Investigator: James C. Freeman, M.D.

Please confirm documented informed consent for 100% of subjects enrolled at the site. The subject records in the NDA submission should be compared to the original documents at the firm. Include a description of your findings in the EIR.

SECTION A

RESERVE SAMPLES: Because these are bioequivalence studies subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and

Page 3 - BIMO Assignment, NDA 202-278 Zecuity (sumatriptan iontophoretic transdermal system) NP101, 6.5 mg

retaining reserve samples from the shipments of drug product provided by the sponsor for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies

(<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples

(<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

Please follow the instructions below:

- Verify if reserve samples were retained according to regulations.**
- If the reserve samples were stored at a third party site, please verify and collect an affidavit to confirm that the third party is independent from the sponsor, manufacturer, and packager, and that the sponsor was notified in writing of the location. In an event the reserve samples were not retained or are not adequate in quantity, please notify the POC immediately.**
- Please obtain a written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a, Affidavit.**
- Samples of the test and reference products in their original containers should be collected and shipped to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening, at the following address:**

Benjamin Westenberger, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101
TEL: (314) 539-2135

SECTION B

Data Audit Checklist:

- Primary pharmacodynamic endpoint data verifiable? _____
- Evidence of under-reporting of AEs identified? _____
- Other endpoint data verifiable? _____
- Evidence of inaccuracy in electronic data capture? _____
- Presence of 100% of signed and dated informed consent forms:_____
- Reports for the subjects audited:_____
- Number of subjects screened at the site:_____
- Number of subjects enrolled at the site:_____
- Number of subjects completing the study:_____
- Verify from source documents that evaluations related to the primary endpoint were accurately reported in case report forms:_____
- Confirm that clinical assessments were conducted in a consistent manner and in accordance with the protocol:_____
- Number of subject records reviewed during the inspection:_____
- SOPs were followed during study conduct:_____
- Examine correspondence files for any sponsor- or monitor-requested changes to study data or reports:_____
- Include a brief statement summarizing your findings (IRB approvals, study protocol and SOPs, protocol deviations, adverse events, concomitant medications, inclusion/exclusion criteria, adequacy of records, drug accountability documents and case report forms for dosing, whether the **randomization schedule was followed for dosing of subjects**, etc.)

- Other Comments:

Collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

Analytical Site:



Investigators:

Bridgette A. Rappe (Study NP101-023)
Diana M. Mathiasen (Study NP101-026)

Methodology:

LC-MS/MS
Analytes: Sumatriptan
Project codes:
XAY (Study NP101-023)
ZTY (Study NP101-026)
Method code: UOJ4
Matrix: Plasma with K₂EDTA
Internal Standard: Sumatriptan-d6
Software: Analyst Version 1.4.2



Please confirm the following during the inspection:

- All pertinent items related to the analytical method used for the measurement of Sumatriptan **concentrations in human plasma should be examined.**
- The accuracy of the analytical data provided in the NDA submission by the applicant should be compared with the original documents at the site.
- **The method validation and the actual assay of the subject plasma samples, the variability between and within runs, QC, demonstration of accuracy and precision in matrix using standards and QCs prepared from separate stocks, stability of subject samples covered by validated stability period.**
- **Use of freshly made calibrators and/or freshly made QCs for stability evaluations during pre-study method validation.**
- **At least one demonstration of precision and accuracy from QCs and calibrators prepared from separate stock solutions.**
- **Scrutinize the number of repeat assays of the subject plasma samples, and the reason for such repetitions, the SOP(s) for repeat assays and if relevant stability criteria like freeze thaw cycles sufficiently covered the stability of reanalyzed subject samples.**

In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Additional instructions to ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to the inspection. Therefore, we request that the DBGLPC POC be contacted for further instructions before the inspection, and also regarding data anomalies or questions noted during review of study records. The ORA investigator should contact the DBGLPC POC for inspection-related questions or clarifications.

Please fax/email a copy of Form FDA 483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations may warrant an OAI classification, please notify the POC as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA 483. Please forward written response as soon as you receive it to Dr. Sam H. Haidar and POC (Fax: 1-301-847-8748 or Email: sam.haidar@fda.hhs.gov).

DBGLPC POC: Jyoti Patel, Ph.D.
jyoti.patel@fda.hhs.gov
Tel: (301)-796-4617
FAX: (301)-847-8748

cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Patel/Mada/Dejernett/CF
OND/ODEI/DNP/Chen, Lana/Bastings, Eric P
OTS/Ocp/DCPI/Bewernitz, Michael
HFR-CE200/ (b) (4)
HFR-CE250/Harris/Henciak, Matt/Smith, Christine (BIMO)
HFR-SW350/ Bromley, Gerald (DIB)/Lopicka, Warren (BIMO)
Draft: JBP 10/12/2012
Edit: SHH 10/12/2012
OSI file #: 6385; O:\BE\assigns\bio202278.doc
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Electronic Archive/BEB
FACTS: **1458728**

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/s/

JYOTI B PATEL
10/12/2012

SAM H HAIDAR
10/12/2012



Food and Drug Administration
Center for Devices & Radiological Health
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

CDRH/ODE Consult Review
NDA 202278

Date: July 18, 2011
To: FILE- CDER and OCP
From: Geeta Pamidimukkala, Biomedical Engineer – DSORD/REDB
Subject: Consult review of NuPathe, Inc. (*sponsor*) NDA submission for the **NP101 Migraine Patch; Sumatriptan Iontophoretic Transdermal Patch** (*device/drug combination*).

Summary/Recommendation:

CDER requested a CDRH consult to review the device component (iontophoresis patch) that was submitted as a combination drug/device product in this NDA. The information provided in this submission is insufficient to demonstrate the device is safe and effective for the proposed intended use. I recommend the sponsor address the deficiencies at the end of this memo in order to proceed with the review of this submission.

I. Submission History

I was the CDRH consult reviewer for NuPathe's IND submission (IND 74,877). The purpose of the IND was to perform a clinical study to evaluate the two design proposals for the NP101 Migraine Patch (iontophoretic transdermal patch) for the treatment of migraine headache with or without aura in adults. The FDA review team met with the sponsor on March 4, 2010 for a meeting to discuss the additional information that would likely be required for a subsequent NDA. In the course of the IND review I informed the sponsor that a separate 510(k) clearance for the patch is not necessary as both the drug and device will be reviewed in the NDA and NDA approval applies to the device component as well. However, should the sponsor wish to market the device alone, without sumatriptan or any other specified drug/ionic solution, the sponsor should submit the device for review in a separate 510(k). NDA approval applies to the combination of the drug and device and cannot be applied to the device separately. The sponsor subsequently submitted this NDA for the use of the NP101 iontophoresis device (trade name: Zelrix Iontophoretic System) for transdermal delivery of sumatriptan for treatment of migraine headache in adults.

CDRH/ODE Review of Device components in NDA submission

The majority of the device information is contained in section 3.2.R.4. The sponsor also provided several attachments with additional information regarding device related information. Below is a complete review of all information regarding the device, except manufacturing, provided within NDA 202278.

II. Device Description

The NP101 (trade name: Zelrix Iontophoretic System) is a prescription use, co-packaged drug/device combination iontophoresis product that is intended to deliver sumatriptan transdermally to treat migraine attacks (with and without aura) in adults. The patch is intended to be applied to the upper arm or thigh. The sponsor refers to the device component of the combination product as the E-Patch. The E-Patch is a disposable, non-sterile, single-use transdermal iontophoresis patch. The E-Patch consists of a microcontroller (b)(4) battery, (b)(4) electrode, and overtape. The microcontroller is pre-programmed to deliver a set current profile over 4 hours (b)(4). Just prior to use the user assembles the system by attaching the drug and salt imbibed pads to the E-Patch (cathode and anode, respectively). This entire assembly is affixed to the user's skin for iontophoretic drug delivery. The current delivery commences once users depress the ON button for 1.5 seconds.

The patch power supply consists of batteries and programmed microcontroller. The device is powered by two (2) (b) (4) batteries that are supplied with the device and housed with the (b) (4) programmed microcontroller. This power supply is encased in a translucent plastic dome (b) (4)

The dome has a button that users press to activate the patch (patch is shipped and stored in sleep mode) and begin current delivery. The power supply also includes a LED to indicate device status (e.g., in use, sleep mode, etc.). Because the plastic dome is translucent, users can see the batteries and the (b) (4) but they are not able to access the batteries or the circuitry.

The electrode is

(b) (4)

(b) (4) foam encircles the electrodes and (b) (4) rings and provides some structure to the patch. The (b) (4) flexible foam is (b) (4) adhesive to adhere to the patient's skin. The top surface of the patch is constructed from cloth woven overtape. The overtape is (b) (4) to adhere to the patient's skin. The (b) (4) foam, overtape, and adhesives are all directly patient contacting.

The device is shipped in Sleep Mode and the LED is off. Users activate the device by pressing the button in the cover dome for a minimum of 1.5 seconds (labeling instructs users to depress and hold the button for 5 seconds). Upon activation the device performs a self test (b) (4)

(b) (4)

The patch is designed to operate within a range of (b) (4) and voltage delivery is up to (b) (4) VDC for (b) (4) (4). The controller monitors current delivery and adjusts voltage to maintain constant current to compensate for changes to skin impedance during Active Mode. The sponsor has calculated the treatment area as the area of the imbibed pads; 30 cm². This correlates to current density of (b) (4) nA/cm² for (b) (4) and (b) (4) nA/cm² for (b) (4).

Safety Features

Several safety features are built into the firmware programmed onto the microcontroller to protect the patient during the dosing period. They are:

- During the (b) (4) the voltage may be increased up to (b) (4) VDC to overcome high skin resistance. This boost in voltage is limited to a maximum of (b) (4) minutes. The maximum current that may be delivered during this boost is (b) (4) milliamps.
- If a current of (b) (4) milliamps is measured for a cumulative (b) (4) minutes during the dosing period the firmware places the E-Patch in Inactive Mode. Current at this level would be measured if the patient had extremely high skin resistance or if the patch was removed before the end of the dosing period.
- During Test Mode or Active Mode if the current exceeds (b) (4) milliamps for a continuous period not to exceed (b) (4) the firmware places the E-Patch in Inactive Mode.
- During Test Mode or Active Mode if the voltage remains above (b) (4) VDC for a continuous period exceeding (b) (4) the firmware places the device in Inactive Mode.

- The electronics are not capable of delivering more than (b) (4) Watts for more than 1 second as a result of any single fault failure condition.

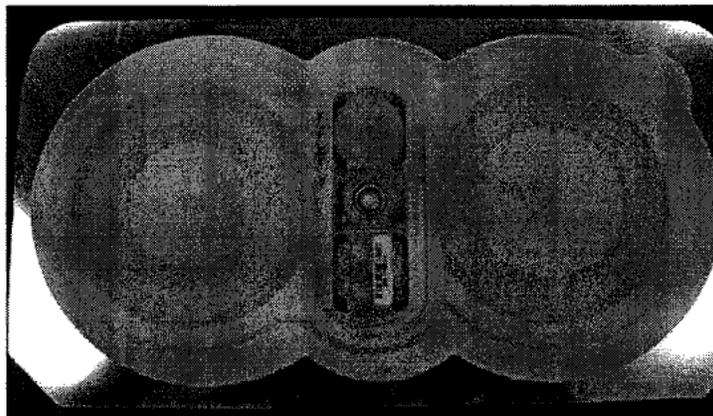


Figure 1: Top view (anode on left): woven overtape and power supply/dome

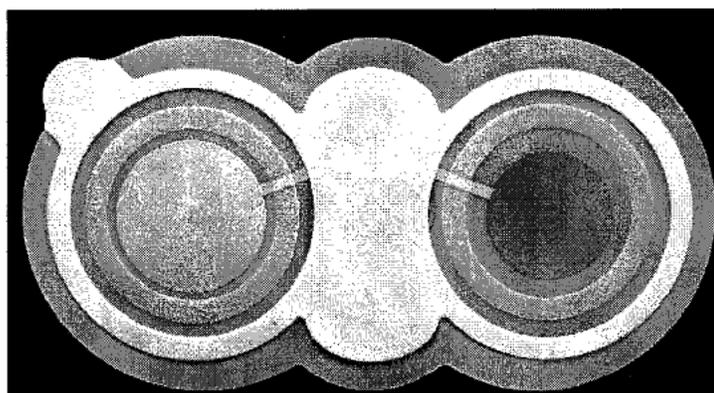


Figure 2: Bottom view (anode on right): electrode, (b) (4) rings, adhesive foam backing

Table 1: Device Summary

Device Characteristic	NP 101
Electrode material	(b) (4)
Electrode area	(b) (4)
Electrode capacity	(b) (4)
Current delivery profile	(b) (4)
Constant current/voltage	(b) (4)
Max output voltage	(b) (4)
Max output power	(b) (4)
Current density*	(b) (4)

	(b) (4)
Power density*	
Operational Impedance Range	
Battery <ul style="list-style-type: none"> Type Capacity 	<ul style="list-style-type: none"> two (2) (b) (4) batteries not specified
Modes	<ul style="list-style-type: none"> <i>Sleep Mode:</i> (b) (4) <i>Test Mode</i> (b) (4) <i>Active Mode:</i> (b) (4) <i>Fail Mode (Inactive Mode):</i> (b) (4)
LED indicator	<ul style="list-style-type: none"> <i>Sleep Mode:</i> (b) (4) <i>Test Mode:</i> (b) (4) <i>Active Mode:</i> solid red <i>Fail (Inactive) Mode:</i> (b) (4)
Single use	Single use, single patient, disposable
Sterile	Provided and used non-sterile

* The listed current density and power density are calculated by reviewer. The sponsor's provided current density is calculated over the area of the imbibed pads, which is greater than the area of the anode and cathode. As it has not been established that the current is evenly distributed over the entire area of the imbibed pads, I have calculated the current and power densities over the area of the anode and cathode, which would represent a worst-case use of the skin contacting the electrodes directly.

Reviewer Comments

- The design of the device is unique as compared to most other iontophoresis patches. Typically, iontophoresis patches are significantly smaller than the subject device. The large electrode size and the relatively low current delivered results in lower current and power density values. The calculated values are well below values that would be likely to result in burns or blistering. The sponsor has calculated the current density based on the size of the drug imbibed pads. It should be noted that the imbibed pads are larger than the electrodes and it is unclear if the current is evenly distributed over the entire drug pad, including the area that is not directly contacting the conductive area of the electrode. The sponsor was asked in the day 74 letter to conduct a dispersion test to demonstrate that the current is evenly distributed over the conductive area of the electrode and over the entire area of the drug pad. The current and power density should be calculated over the area on which current is delivered to the patient. FDA recommends that the maximum power density of stimulating electrodes should be less than 250 mW/cm² to reduce the risk of thermal burns. Power density should be calculated using the

Market Packaging: The pouches are shipped in cartons constructed from (b) (4). The units are available in (b) (4) 6 pack cartons. The packaging passed the International Safe Transit Association (ISTA) integrity performance test 1C to verify the marketed package can withstand the rigors of the shipping distribution environment without affect to the function of the product.

Reviewer Comments:

1. The information regarding the E-Patch packaging is adequate. The packaging of the imbibed pads (i.e., the reservoir card) is reviewed by CDER as the pads are the drug component.
2. Internally, there was some concern of the potential for static from the transparent (b) (4) sheet to affect the (b) (4). The sponsor has completed evaluation of the device per IEC-60601-1 and demonstrated the device is immune to electrostatic discharge.
3. It is worth stating that a previously approved iontophoresis combination product, the Ionsys iontophoresis device (NDA 21-338, IND (b) (4)). For the subject device, the potential for circuitry degradation due to excessive moisture within the packaging is unlikely because the imbibed pads with are sealed and contact between the pads and E-Patch is unlikely. Additionally, the sponsor found that high ambient humidity (75% RH) did not affect the performance of the device in the shelf life evaluation.
4. Note, the packaging used for the NP101 clinical evaluations is slightly different than the proposed marketing packaging. A plastic holder was used to hold the E-Patch (b) (4) during the clinical evaluations. This difference is unlikely to impact product safety or effectiveness as the packaging material is inconsequential to the performance of the device. This difference may impact device usability, however. As such, the sponsor has conducted a usability study which is reviewed by CDER.

IV. Labeling

The sponsor has provided product labeling in Section 1.14 of the original submission. The product is referred to by its trade name within the labeling; ZELRIX. The labeling contains contraindications, warnings, precautions, and adverse reaction information, but does not differentiate between those associated with the drug and the device. Below is a brief summary of the elements within the labeling that I have identified as being primarily associated with the device component.

- *Indications:* The labeling includes the appropriate indications for use (transdermal delivery of sumatriptan for the acute treatment of migraine attacks, with or without aura, in adults). (b) (4)
- *Administration/Dosing:* (b) (4)
- *Contraindications:* (b) (4)
- *Warnings & Precautions:* (b) (4)
- *Adverse Reactions:* (b) (4)
- *Storage info: (section 16)* (b) (4)
- *Expiration:* will be labeled with (b) (4) expiration (see shelf life evaluation below)
- *Contact info:*
- *Rx use only*
- *Disposal:* There are no specific disposal instructions. The device component can be disposed of in regular household trash.

Patient Labeling begins in section 17.8 of the labeling section. This section includes patient instructions for use.

1. The reviewed labeling information provided in Section 1.14 does not include the carton labeling. This should be provided for review. Also- the device labeling should include the prescription statement in accordance with 21 CFR 801.109(b)(1)
2. Patient labeling section:
 - (b) (4) It may be worth adding an explanation that if the light turns off before 4 hours the device, the full 6.5 mg may not have been delivered.
 - Under "How should I use ZELRIX" heading: states (b) (4) " This reads that users can have 2 patches active at the same time.
3. (b) (4)
4. *Warnings/Precautions:* (b) (4)
5. For reference, the other NDA approved iontophoresis system IONSYS (NDA 21-338) labeling included the

following statements:

- the system should be removed before cardioversion or defibrillation to avoid damage to the system from the strong electromagnetic fields set up by these procedures.
- device contains radio-opaque components and may interfere with an X-ray image or CAT scan.
- The low-level electrical current provided by IONSYSTM does not result in electromagnetic interference with other electromechanical devices like pacemakers or electrical monitoring equipment.
- the labeling indicated that the current delivery is generally imperceptible.
- Instructed not to place patch on abnormal skin sites; scars, burns, tattoos

V. Sterilization/Shelf Life/

Sterility: The NP101 co-packaged drug/device combination product is not being marketed as a sterile device or system. The device is packaged, supplied, and used non-sterile.

Shelf Life: sponsor states the 6 month realtime stability evaluation in commercial packaging and 9 months real time stability evaluation in clinical packaging supports extrapolation to (b) (4) shelf life from date of manufacture (reference Release Specification document provided in Amendment 0003, 3.2.P.5.1).

Stability studies are underway with NP101 to address shelf life. These stability studies are detailed in Section 3.2.P.8 of the NDA.

- Stability data for co-packaged product in commercial packaging is available through 6 months. Section 3.2.P.8.1.4 (original submission) outlines the evaluations of the device performance on the commercially packaged system evaluated over 6 month time period. Samples evaluated at initial release, 1, 2, 3, and 6 months at accelerated (40oC/ 75% RH), CRT (25 oC/60% RH) at initial, 3 and 6 months, and intermediate (30 oC/ 65% RH) at initial and 6 months. The sponsor evaluated the (b) (4) (per NuPathe method TM-0002) and (b) (4) (per SOP CM 013) of the device component to demonstrate that the device performance is unaffected by storage. All testing met specifications. Evaluated Lot #: MBR-75-NP101-017-0001
- Stability data for co-packaged product in clinical packaging is available through 9 months. Section 3.2.P.8.1.5 (original submission) outlines the evaluations of the device performance on the clinically packaged system evaluated over 9 months. Samples were evaluated at 3 and 6 months at accelerated (40 oC/ 75% RH). Samples were evaluated at initial, 3, 6, and 9 months with CRT (25 oC/ 60% RH). Samples were evaluated at intermediate conditions (30 oC/ 65% RH) at 6 and 9 months. (b) (4) were tested at each evaluated time point. All testing met specifications. Evaluated Lot #: MBR -75-NP101-007-0012.

Amendment 16 (6/21/11)- the sponsor provided a (b) (4) report to demonstrate that the storage orientation (flat, side, etc) does not have a material impact on pad saturation or drying. The provided information is adequate.

Reviewer Comments

1. The conducted shelf life testing on the clinical and commercially packaged system (9 months and 6 months, respectively) can be used to support an expiration date of (b) (4) months, however the sponsor should address the following:
 - NuPathe Stability Protocol for NP101 Documents for Device Stability, Lot MBR-75-NP101-007-0012 and Lot MBR-75-NP101-017-0001 (Document Nos: Prot-CM-NP101-007, and Prot-CM-NP101-008, respectively) state the protocol was amended to (b) (4)
 - The sponsor has included a document in section 3.2.P.8.2 of the original submission titled "Post-approval Stability Protocol and Stability Commitment." This document states the sponsor will (b) (4)
- . The sponsor should provide a rationale for why

these evaluations will not be conducted.

- The sponsor should provide the pass/fail criteria for the (b) (4)

Note- the sponsor also evaluated the drug reservoir stability and the adhesive stability. These evaluations were reviewed by CDER.

2. It is worth stating that the actual age of the lot for the Reservoir Card that was evaluated in the co-packaged stability studies (both clinical and commercial) was greater than that at the time of the pull. (12 months for clinical, 15 months in commercial). This does not affect the device performance evaluations because the reservoir card was not utilized in the device performance tests. The sponsor evaluated only the electrode capacity and the current delivery profile over 4 hours. In both the clinical and commercial co-packaged evaluations, the performance of the device met acceptance criteria. It is anticipated that because the sponsor has demonstrated that electrode charge capacity is unchanged and the device is able to consistently deliver current appropriately over the 4 hour delivery time, the device will be unaffected by storage. The shelf life evaluations are acceptable.
3. The shelf life validation should also evaluate the potential for corrosion (or other break down) of the power supply (ie (b) (4) & batteries)

VI. Biocompatibility

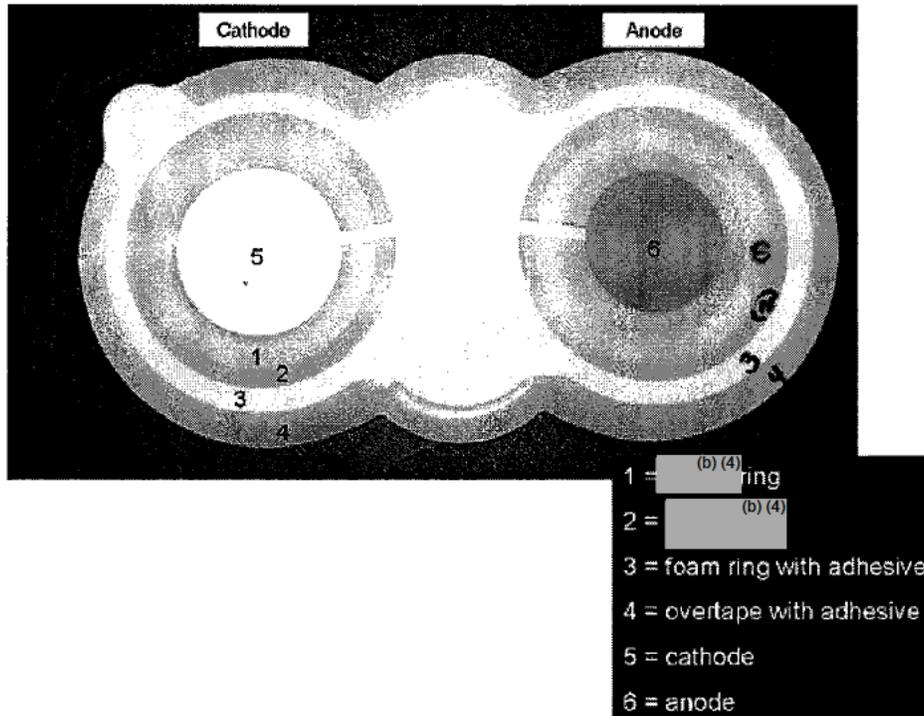
The sponsor has identified the following materials used in construction of the E-Patch as having direct contact to the patient:

- (b) (4) adhesives (b) (4) onto the foam and the overtape.
- Foam
- Overtape
- (b) (4) film
- (b) (4) pad transfer ring

According to ANSI/AAMI/ISO 10993-1:2003 Table 1, the E-Patch is considered a skin surface contacting device with limited contact duration. As such, all patient contacting components of the patch should be evaluated for cytotoxicity, sensitization, and irritation or intracutaneous reactivity. Biocompatibility studies that have been performed with the foam, overtape, (b) (4) film, and (b) (4) pad transfer rings. The test article was identified in each report as the E-Patch (with (b) (4) removed). Testing of (b) (4) ((b) (4) , pad transfer ring ((b) (4) ring), overtape with adhesive ((b) (4) and foam. The tests were conducted at an independent contract laboratory. The tests were performed under GLP regulations (21 CFR 58) and in accordance to SOP and a standard protocol. All biocompatibility reports are located in the Toxicology section of the original NDA submission (section 4.2.3.7.7). Complete reports were provided for the following assays:

- Cytotoxicity: ISO 10993-5:1999- "*Biological Evaluation of Medical Devices, Part 5: Tests for in vitro cytotoxicity.*" The assay evaluated the in vitro toxicity of the test article to mammalian cells when leachable extracts were allowed to diffuse through an agarose barrier and contact cultured cells. L-929 mouse fibroblast cells were utilized for this assay. The positive control, negative control, and test articles (1 cm x 1 cm) were placed in the agarose culture in triplicate and incubated for 24 hours. The control samples and test articles were removed from the culture and the culture was stained and evaluated for cell lysis. The test article showed no signs of lysis under or around the test area (score 0). The positive control had a score of 4 (toxic) and the negative control had a score of 0 (non-toxic). The results are valid.
- Irritation: ISO 10993-10:2002- "*Biological Evaluation of Medical Devices, Part 10- Tests for irritation and sensitization*"- test article and negative control patches (6 of each) were applied to the shaved skin of 3 adult albino rabbits for four hours. Observations for skin irritation were conducted at 60 minutes, 24 hours, 48 hours, and 72 hours after removal of patches. One animal had a score of 1 (very slight erythema) at the 24 hour mark on the right side. This resulted in a primary irritation score of 0.2 for this animal. The overall primary irritation score for the test article is 0.1, which is negligible. The results conclude that the test article elicits negligible irritation response.
- Dermal Sensitization: ISO 10993-10:2002 "*Biological Evaluation of Medical Devices- Part 10: tests for*

irritation and delayed type hypersensitivity” Repeated Patch Dermal Sensitization Test (Buehler method, modified for longer induction exposure for test article). 10 guinea pigs patched with test article, 5 guinea pigs patched with negative control for 6 hours of exposure followed by 24 hour rest period and observed for erythema and edema. The procedure was repeated 3 times per week for 3 weeks (total of 9 applications). Following a 2 week rest period the animals were patched with the respective test article (test article on test animals and control article on control animals). The patches were removed after 6 hours exposure. Patch sites were observed for erythema and edema at 24 hours and 48 hours after patch removal.



Reviewer Comments

1. The test article in each report is described as the “E-Patch (with (b) (4) removed); testing (b) (4) pad transfer ring, overtape with adhesive, foam barrier with adhesive.” For clarity, the sponsor should state if the evaluated test articles are the final device materials intended for commercial marketing.
2. I discussed the completed tests with Joseph Neilsen, PhD, the biocompatibility expert in CDRH/ODE/DSORD. He determined that the completed testing is adequate. A formal consult was not requested.

VII. Software/ Firmware

The device uses firmware preprogrammed onto the microcontroller. The firmware cannot be modified or accessed by the patients or physicians. The sponsor has identified the firmware as having a major level of concern because it is intended to be used in combination with a drug. The microcontroller is (b) (4). The firmware is written using (b) (4) code. The purpose of the firmware is to (b) (4) 4 hour dosing period.

The software (firmware) is determined to have a MAJOR level of concern because the device is intended to be used in combination with a drug. Note, the release version of the firmware is Version (b) (4).

The firmware controls the following functions (as described in the SRS (attachment 18) document in the original submission):

- *Sleep Mode* – [REDACTED] (b) (4)
- *Self Test* – [REDACTED] (b) (4)
- *Test Mode* – [REDACTED] (b) (4)
- *Active Mode* – [REDACTED] (b) (4)
- *System Timing* – [REDACTED] (b) (4)
- *Current delivery* – [REDACTED] (b) (4)
- *Self Test Fail Mode* – [REDACTED] (b) (4)
- [REDACTED] (b) (4)

The sponsor has provided all applicable software documentation in section 8 of 3.2.R.4 of the original submission. Per CDRH Guidance document for the Content of Premarket Submissions for Software Contained in Medical Devices, the sponsor has provided the following documentation for devices that contain software having a MAJOR level of concern:

- Software Requirements Specifications (SRS): (attachment 18: software requirements specification review report)- the sponsor provided the SRS document (with amendments) for the functional requirements for each mode: sleep mode, self test, test mode, active mode, and self test fail mode. The SRS Review Report notes the fixes for anomalies observed in software version (b) (4). There are no unresolved anomalies.

- Architecture Design Chart: (attachment 19)- the sponsor provided an adequately detailed Software Architecture Design Document (SADD)- which incorporates the SDS documentation. The sponsor has provided state flow charts. There are some minor typographical errors that were noted in the document that will be addressed after updates. There are no unresolved anomalies noted.
- Software Design Specification (SDS) (attachment 19)- the sponsor has combined the SDS and architecture design chart into 1 document which they refer to as SADD. The document includes detailed description of the software modules/states and includes code for each state. Note- speed up mode is used during testing and not available during clinical use.
- Traceability Analysis: (attachments 20, 21, 22)- the sponsor provided multiple traceability documents. Attachment 20: linking SRS to the test case and test procedures documents. Attachment 21: linking SADD to Source Code Verification document. Attachment 22: linking software hazards to SADD (see Hazard Analysis section of memo below).
- Software Development Environment Description: In section 8.8 of 3.2.R.4 (original) the sponsor outlines the software development process. The firm used an evolutionary development strategy; continually modifying the software during the development process as new requirements and safety factors were identified. Clinical evaluation of the software was initiated only following satisfactory evaluation in bench evaluations. Subsequent modifications were made following new issues identified during clinical use. The microcontroller had undergone 4 generational changes.
- Verification & Validation: The sponsor provided the test procedure and log for all completed V&V evaluations. It is not clear if all V&V evaluations were conducted on the system version to be commercially available.
- Revision Level History: The sponsor provided a memo in attachment 48 from (b) (4), the firm contracted to develop and test the software, which states the final version of the software is version (b) (4). The memo also states that the modification made in (b) (4) from version (b) (4) was a change in (b) (4) (change removed a (b) (4)). The change was prompted by the microprocessor which is designed with (b) (4). The change does not affect operation of the device and the completed validation on version (b) (4) is applicable to version (b) (4). Version (b) (4) was only evaluated per the Fast test and the 4-Hour test.
- Unresolved Anomalies: The sponsor states there are no unresolved anomalies in release version (b) (4).

1. There is a discrepancy in the nomenclature used for the modes. The architecture design report states the device (b) (4). Sponsor should clarify if wake-up mode is the same as self test mode.
2. Is there a time-out limit in Self-Test mode to detect the battery voltage range before either proceeding (b) (4).
3. It is not clear if the device stays in Test Mode for a (b) (4).
4. How many times can the patch enter sleep mode (b) (4)?
5. The arch design report lists a (b) (4) mode” What is this?
6. The sponsor has completed all of the V&V activities on firmware version (b) (4), however the patch will be commercially released with version (b) (4). A full validation of version (b) (4) was not completed. The sponsor provided a rationale from (b) (4) (attachment 48) that the difference between the 2 versions is not expected to impact performance and version (b) (4) did pass the “(b) (4) test and the (b) (4)” test. It is not apparent which of the tests were performed and why only these 2 tests were evaluated.

VIII. EMC & Electrical Safety

In section 2 of 3.2.R.4 (original submission) the sponsor declares conformity to the following electrical safety standards.

- IEC 60601-1-2 (2001): Medical Electrical Equipment- Part 1: General requirements for safety; Electromagnetic compatibility requirements and tests.

Electromagnetic Compatibility evaluation was conducted by a contract lab; (b) (4) The test report was included in Attachment 49. The report evaluated the following:

- Radiated Emissions: IEC 60601-1-1 (2007) Group 1 Class B
- Electrostatic Discharge: IEC 61000-4-2 (2008)
- Radiated Immunity: IEC 61000-4-3 (2008)
- Magnetic Immunity: IEC 61000-4-8 (2009)
- IEC 60601-2-2 (2006): Medical electrical Equipment- Part2-2: Particular requirements for the safety of high frequency surgical equipment

Reviewer Comments:

1. It is not clear why the sponsor states conformity to IEC 60601-2-2. This standard is not applicable because the device does not deliver or generate high frequency current. It appears that the sponsor had completed the patch conformability evaluation according to this standard, but the sponsor should provide a statement to which parts of the standard the device conforms to.

IX. Performance Testing

- Bench Testing/Performance Verification
 - *Power supply performance verification* (Attachment 50)- variable resistance, maximum resistance conditions to evaluate correct device output and performance. This test is conducted to verify power supply performance.
 - *Power Source Verification* (attachment 52): evaluation of battery performance. Battery should meet prespecified power and capacity requirements (based on power requirements for proper device performance). This report outlines the various batteries tested and how the (b) (4) battery was selected.
 - *Electrochemical capacity of electrodes* (amendment 7, Doc # TM-0002.04)- evaluation of anode and cathode electrode capacity to ensure the electrodes will be able to have at a minimum capacity of (b) (4) mA-min to ensure proper use of the device.
 - *Conformability* (attachment 55)- at the request of FDA (during pre-NDA meeting 3/4/2010) requesting evaluation of the patch conformability to thigh and arm. During this meeting I suggested the firm reference ANSI/AAMI HF 18 for guidance in method development. That standard is no longer recognized by the Agency and is superseded by IEC 60601-2-2. The sponsor used this standard for test method development. The standard evaluated conformability to user forearm for worst case (5 females, 5 males). The patch was left on the arm for 1 hour. All patches had less than (b) (4) lift.
 - *Current Density*: in the Day 74 letter, I had requested the sponsor complete a dispersion test or equivalent to ensure that the current is evenly distributed over the area of the electrodes and that there is no area of unintended focal current during normal current delivery that could result in burn or injury to the user. The sponsor responded with FEA models for 3 scenarios: 1) intended use (where drug pad and salt pad completely cover the anode and cathode, respectively), 2) unintended use #1 (where the device is operated without the pads; anode and cathode directly contact the skin), 3) unintended use #2 (where drug pad and salt pad are misaligned; 25% of each electrode is in direct contact with skin). It was determined that the highest degree of non-uniform current density distribution occurs at (b) (4), with decreasing non-uniformity as contact resistance increases. Models revealed that current density is non-uniform between anode/drug pad and cathode/salt pad surfaces (with increasing current density towards outer edge of electrode). The non-uniform distribution is less evident at the skin surface.
- Animal:
 - The sponsor conducted several dermal tolerance evaluations using pig model.
- Clinical: Pivotal study with 530 human subjects, multi-center, randomized, parallel group, double blind,

placebo controlled trial established efficacy and tolerability. The clinical studies were evaluated by CDER.

Reviewer Comments

1. The completed bench tests are adequate. The performance of the device has been adequately verified.
2. The completed FEA modeling evaluation of current density distribution is adequate. It is common to see increased current density at the outer edges of the electrodes. The limitations of the maximum current reduce the likelihood of this non-uniform distribution to result in patient injury.
3. The use of the pig model for the animal tolerance tests is adequate. The pig model is frequently used as animal model for human skin, particularly for RF dermatological evaluations.
4. The clinical study reports were evaluated within CDER. I reviewed these reports and found that the most commonly occurring adverse events (site pain, site pruritus) are typical for iontophoresis devices.

X. Hazard Analysis

The device hazard analysis (Attachment 17: Software Safety Report and Review Report) was performed by (b) (4) during the verification and validation of the firmware. ISO 14971:2007, "Medical Devices – Application of Risk Management to Medical Devices," and IEC 62304:2006, "Medical Device Software – Software Life Cycle Processes" were referenced for the analysis.

Reviewer Comments

The provided hazard analysis is incomplete and inadequate. The sponsor evaluated only hazards associated with software. The sponsor should identify and evaluate hazards associated with hardware failure, operational error, etc.

XI. Deficiencies to be conveyed to the sponsor

Device Description

You state that the E-Patch is powered by 2 (b) (4) batteries. Please provide the battery specification sheet, which should include the battery capacity.

Labeling

The provided labeling information included in Section 1.14 does not include the carton labeling. Please submit the primary carton/pouch labels for review.

The Patient labeling section includes the following statement; (b) (4)
(b) (4) Please add a statement explaining that if the light turns off before 4 hours, the full 6.5 mg sumatriptan does may not have been delivered.

In the Patient Labeling section under the "How should I use ZELRIX" heading, states (b) (4)
(b) (4) This statement can be interpreted to mean users can apply 2 active patches simultaneously. Please revise this statement to make clear that users may apply a second patch following shut down of the first patch.

Please add the following contraindication: for patients with known sensitivity or adverse reaction to application of electrical current

Please add the following to the Warnings/Precautions sections of your labeling: "patch can be worn during normal activity, however excessive motion may cause poor contact between skin and electrodes. This may result in uneven distribution of current increasing the risk of skin irritation." Additionally, please add a statement instructing users to remove the patch if they experience a burning sensation during use.

Stability/Shelf Life

You evaluated the performance of the clinical and commercially packaged system after 9 months and 6 months storage, respectively, to support an expiration date of (b) (4) months. Please address the following:

- a) NuPathe Stability Protocol for NP101 Documents for Device Stability, Lot MBR-75-NP101-007-0012 and Lot MBR-75-NP101-017-0001 (Document Nos: Prot-CM-NP101-007 and Prot-CM-NP101-008, respectively) state the protocol was amended to (b) (4).
(b) (4)
- b) You included a document in section 3.2.P.8.2 of the original submission titled "Post-approval Stability Protocol and Stability Commitment." This document states that (b) (4).
(b) (4)
Please provide a rationale for why these evaluations will not be conducted.
- c) Please provide the pass/fail criteria for the (b) (4).
- d) Please clarify to what extent your shelf life validation evaluated the potential for corrosion (or other break down) of the power supply.

Biocompatibility

You provided the test reports from the completed cytotoxicity, irritation, and dermal sensitization evaluations to demonstrate biocompatibility of patient contacting device components. The test article in each report is described as the "E-Patch (with (b) (4) removed); testing (b) (4) pad transfer ring, overtape with adhesive, foam barrier with adhesive." Please state if the evaluated test articles are identical to the final device materials intended for commercial distribution. Please be advised that biocompatibility should be established for the device you intend to market.

Software/Firmware

You list and describe the following modes in the software description section of your submission (section 8.2 of 3.2.R.4): sleep mode, self test, test mode, active mode, self test fail mode, (b) (4) mode. There are discrepancies in the naming convention and description of each mode within the software related documents you provided in attachments 17-48. Please address the following:

(b) (4)

Please address the following regarding the "self test," "test," and "active" modes:

(b) (4)

Please state what is the expected result if the On button is depressed at any point once the device is no longer in Sleep mode.

The Hazard Analysis you provided in attachment 17 of the original submission identified hazards associated with firmware or hardware failure. Please address the following:

- a) This is an incomplete analysis as you did not evaluate potential hazards associated with use of the device in other categories (e.g., electrical, operational, environmental, mechanical). Please update your hazard analysis to include all potential hazards that result from device use. Alternatively, you may provide a rationale for why you have omitted identification and evaluation of other hazards from your analysis.
- b) Burns and blistering are commonly reported adverse events for iontophoretic drug delivery patches, however you did not identify this hazard in the Hazard Analysis. Please update the hazard analysis to include this risk and all potential causes, along with appropriate mitigating actions.
- c) You provided several samples of the system for review. The drug and salt patches have a very similar appearance and it is possible for users to inadvertently switch the anode and cathode patches. Please address the potential for such an occurrence and discuss the potential hazards to the patient. Please update the Hazard Analysis accordingly.
- d) The Software Safety Report in attachment 17 states the analysis was performed on software Version (b) (4). Please clarify if all risk controls identified in the Hazard List table have been implemented in the software Version (b) (4) the version that is intended for commercial distribution.

You have completed all of the validation and verification activities on firmware version (b) (4), however the E-patch will be commercially released with version (b) (4) and a full validation of this version was never completed. You provided a memo in attachment 48 which states that the differences between the two versions are not expected to impact performance and that version (b) (4) passed the (b) (4) test and the (b) (4) test. Please provide the test report (method, results, discussion) for these completed tests and provide a rationale for why these two tests alone are sufficient. Alternatively, please complete a full validation and verification of the firmware version you intend to use in the commercial product.

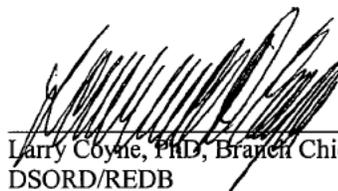
Testing

In section 2 of 3.2.R.4 of the original submission you declare conformity to several standards, including IEC 60601-2-2 (2006); Medical Electrical Equipment Part 2-2: Particular requirements for the safety of high frequency surgical equipment. It is not apparent how this standard is applicable to your device as your device does not generate or deliver high frequency current. Please explain the extent to which your device conforms to this standard.

 7/18/11

Geeta Pamidimukkala, MS, Biomedical Engineer
Restorative Devices Branch
Division of Surgical, Orthopedic, and Restorative Devices

Attachment:

 Date: 7/18/11
Larry Coyne, PhD, Branch Chief
DSORD/REDB

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

/s/

CAROLINE STRASINGER
07/20/2011

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

REVIEW DEFERRAL MEMO

Date: Junly 1, 2011

To: Russell Katz, M.D., Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

Melissa Hulett, MSBA, BSN, RN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Robin Duer, MBA, BSN, RN
Senior Patient Labeling Reviewer
Division of Risk Management

Subject: Review Deferred: Patient Labeling (Medication Guide,
Instructions for Use)

Drug Name(s): ZELRIX (sumatriptan) Iontophoretic Transdermal
System

**Application Type/
Number:** NDA 202278

Applicant/Sponsor: NuPathe, Inc.

OSE RCM #: 2011-48

This memorandum documents the deferral of our review of ZELRIX (sumatriptan) Iontophoretic Transdermal System. On January 10, 2011, the Division of Neurology Products (DNP) requested that the Division of Risk Management (DRISK) review the Patient Labeling (Medication Guide, Instructions for Use) for ZELRIX.

Due to outstanding Chemistry deficiencies, DNP plans to issue a Complete Response (CR) letter. Therefore, DRISK defers comment on the Applicant's proposed patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the CR letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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

/s/

ROBIN E DUER
07/01/2011

LASHAWN M GRIFFITHS
07/01/2011

MEMORANDUM

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

DATE: June 28, 2011

TO: Russell G. Katz, M.D.
Director, Division of Neurology Products

FROM: Charles R. Bonapace, Pharm.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

(b) (4)
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Martin K. Yau, Ph.D.
Acting Team Leader - Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 202-278, Zelrix
(sumatriptan) Iontophoretic Transdermal Patch,
sponsored by NuPathe Inc.

At the request of the Division of Neurology Products, the Office of Scientific Investigations (OSI), Division of Bioequivalence and GLP Compliance conducted audits of the clinical and analytical portions of the following bioequivalence study:

Study Number: NP101-013

Study Title: "A Phase I, Single Center, Open Label, Randomized, Single-Dose, Three-Way Crossover Study to Compare the Pharmacokinetics and Bioavailability of Three NP101 (Sumatriptan Iontophoretic Transdermal Patch) Treatments With an Oral Formulation of Imitrex® in Healthy Volunteers and to Collect Resistance Data During Application of NP101"

The clinical portion of the study was conducted at Prism Research, LLC, St. Paul, MN. Following the inspection at Prism Research (June 13-24, 2011), Form FDA 483 was issued (Attachment 1). No written response for the Form FDA 483 observations has been received yet. OSI will review and forward any responses when they are received.

The analytical portion of the study was conducted at (b) (4). Following the inspection at (b) (4), Form FDA 483 was issued (Attachment 2). OSI received the response to the Form FDA 483 on May 9, 2011 (Attachment 3). Our evaluation of the Form FDA observations at both sites and the response from (b) (4) follow:

Prism Research, LLC, St. Paul, MN

1) Failure to maintain adequate case histories with respect to informed consent. Specifically, informed consent documents, the version approved by the reviewing IRB on 1/28/2010, were not on file for subjects 007, 016 and 020.

Although the latest approved version of the consent form was not on file for three subjects, it is unlikely that this impacted the outcome of the study. OSI recommends that this observation is unlikely to have significant impact on data integrity or subject safety.

2) Failure of firm to retain reserve samples of the test articles and of the reference standard used to conduct the aforementioned study. Specifically, test articles NP101B and NP101D and reference standard NP101A were not collected and retained at the clinical site.

Prism Research failed to retain reserve samples for the test (NP101B and NP101D) or the reference (NP101A) products. Without the reserve samples, there is no assurance of the identities of the products used to dose subjects in the study. Furthermore, it is not permissible to replace the missing reserves from other materials.

(b) (4)

1) Failure to reject calibrators at concentrations #7 and #8 in sumatriptan method validation runs 1UOJ4-B and 2UOJ4-A when they were prepared or labeled incorrectly.

(b) (4) prepared nine concentrations of calibrators in bulk and aliquotted them into vials for daily use during the method validation. Because the back-calculated concentrations of calibrators #7 and #8 in runs 1UOJ4-B and 2UOJ4-A appeared to be reversed, the (b) (4) analyst exchanged their labels for calculations, discarded the remainder of the #7 and #8 calibrator vials, and prepared them again in fresh batches for use in later runs. However, there were no records to justify the label exchange. During the inspection, we requested that (b) (4) recalculate the calibration curves for these runs, excluding the questionable calibrators #7 and #8. The runs' validation data were within acceptance criteria (included within Attachment 3). OSI recommends using the recalculated validation data from runs 1UOJ4-B and 2UOJ4-A for DNP reviews.

2) Failure to document error investigations completely and promptly, regarding calibrators #7 and #8 in the sumatriptan method validation experiments under projects UOJ4 and UOJ5.

(b) (4) acknowledges improper handling of the suspected errors, and failure to conduct and document a timely investigation. However, (b) (4) later implemented SOP LP-BA-024, Laboratory Investigations, and assures OSI that it will prevent recurrence of similar events.

Conclusion:

OSI recommends that the analytical data generated at (b) (4) be accepted for review. However, OSI cannot assure the identity of the test and reference drug products used to dose subjects in this study at Prism Research. OSI recommends that the data from NP101-013 generated at Prism Research are not acceptable for review.

Page 4 - NDA 202-278, Zelrix (sumatriptan) Iontophoretic
Transdermal Patch

After you have reviewed this transmittal memo, please append it
to the original NDA submission.

Charles R. Bonapace, Pharm.D.
Pharmacologist

(b) (4)
Pharmacologist

Final Classifications:

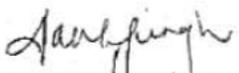
OAI - Prism Research, LLC, St. Paul, MN
(FEI Number: Not available)

NAI - (b) (4)

cc: DARRTS

CDER DSI PM TRACK
OSI/Ball/Salewski
OSI/Haidar/Yau (b) (4)/Dejernett/Bonapace/CF
DNP/Katz/Todd/Bastings/Chen
OCP/Men/Parepally
HFR-CE2545/McNew
HFR-CE8590/Singh
Draft: CRB 6/27/11
Edit: MFS 6/27/11
DSI: 6173; O:\BE\EIRCover\202278.nup.sum.doc
FACTS: 1258517

Attachment 1. Form FDA 483 from Prism Research, LLC

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT OFFICE ADDRESS AND PHONE NUMBER		DATE(S) OF INSPECTION	
450 Marquette Avenue, Suite 600 Minneapolis, MN 55401 (612) 534-4100		6/13-15, 20-22, 24/2011	
Industry Information: www.fda.gov/oc/industry		FBI NUMBER	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED			
TO: Dr. Ron M. Canas, MD, Clinical Investigator			
FIRM NAME		STREET ADDRESS	
Prism Research, LLC		1000 Westgate Drive, Suite 149	
STATE AND ZIP CODE		TYPE OF ESTABLISHMENT INSPECTED	
St. Paul, MN 55114		Biopharmaceutics Clinical Facility	
<p>THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.</p> <p>DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:</p> <p>For a study titled, "A Phase I, Single Center, Open Label, Randomized, Single-Dose, Three-Way Crossover Study to Compare the Pharmacokinetics and Bioavailability of Three NP101 (Sumatriptan Iontophoretic Transdermal Patch) with an Oral Formulation of Imitrex in Healthy Volunteers and to Collect Resistance Data During Application of NP101":</p> <p>Failure to maintain adequate case histories with respect to informed consent. Specifically, informed consent documents, the version approved by the reviewing IRB on 1/28/2010, were not on file for subjects 007, 016 and 020.</p> <p>Failure of firm to retain reserve samples of the test articles and of the reference standard used to conduct the aforementioned study. Specifically, test articles NP101B and NP101D and reference standard NP101A were not collected and retained at the clinical site.</p>			
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Tara C. Singh, Consumer Safety Officer	06/24/2011

COPY

Attachment 2. Form FDA 483 from (b) (4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		
DISTRICT OFFICE ADDRESS AND PHONE NUMBER (b) (4)		DATE(S) OF INSPECTION (b) (4)
Industry Information: www.fda.gov/oc/industry		FEI NUMBER (b) (4)
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: (b) (4)		
FIRM NAME (b) (4)	STREET ADDRESS (b) (4)	
CITY, STATE AND ZIP CODE (b) (4)	TYPE OF ESTABLISHMENT INSPECTED Bioanalytical Laboratory	
<p>THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.</p> <p>DURING AN INSPECTION OF YOUR FIRM (I) <input checked="" type="radio"/> (WE) OBSERVED:</p> <p>In regard to study PROT-15-NP101-013:</p> <ol style="list-style-type: none"> 1) Failure to reject calibrators at concentrations #7 and #8 in sumatriptan method validation runs 1UOJ4-B and 2UOJ4-A when they were prepared or labeled incorrectly. 2) Failure to document error investigations completely and promptly, regarding calibrators #7 and #8 in the sumatriptan method validation experiments under projects UOJ4 and UOJ5. 		
SEE REVERSE OF THIS PAGE	(b) (4)	EMPLOYEE(S) NAME AND TITLE (Print or Type) (b) (4)
		DATE ISSUED (b) (4)

Attachment 3. Responses for Form FDA 483 observations from Development LP (b) (4)

(b) (4)

(b) (4)

Sam H Haidar, Ph.D., R.Ph., Chief, GLP and Bioequivalence Investigations Branch
Division of Scientific Investigations, Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5330
10903 New Hampshire Ave
Silver Spring, MD 20993

Re: Response to FDA 483 Observations (b) (4)
(b) (4)

Dear Dr. Haidar:

Enclosed is a copy of the letter sent to (b) (4), Director of the FDA (b) (4) District Office in response to the FDA 483 that was issued to (b) (4) following the (b) (4) inspection at the bioanalytical laboratory in (b) (4). At the inspectional exit meeting Dr. (b) (4) requested that the response be provided to you. If you have questions regarding the response please contact me at (b) (4), extension (b) (4)

Sincerely,

(b) (4)

Enclosure

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Re: Response to FDA 483 Observations (b) (4)
(b) (4)

Dear Ms. (b) (4)

Enclosed is (b) (4) response to the FDA 483 that was issued following the (b) (4) inspection at (b) (4)

We would appreciate it if you would include this response with any Freedom of Information releases of the FDA 483. If you have questions regarding the response please contact me at (b) (4), extension (b) (4)

Sincerely,

(b) (4)

Enclosure

cc: Sam H Haidar, Ph.D., R.Ph., Chief, GLP and Bioequivalence Investigations, FDA

(b) (4)

(b) (4)

Response to FDA483 Observations Issued (b) (4)

FDA483 Observations

In regard to study PROT-15-NP101-013:

1) Failure to reject calibrators at concentrations #7 and #8 in Sumatriptan method validation runs 1UOJ4-B and 2UOJ4-A when they were prepared or labeled incorrectly.

Response:

Full validation of the assay for analysis of sumatriptan in human plasma was conducted in 2002. A partial validation under (b) (4) project code UOJ4 was conducted in 2004 to provide validation data for support of an LC-MS/MS instrument platform change from a Micromass Micro to a Sciex 3000 instrument. For the purpose of partial validation between instruments, calibrator pools were prepared at nine concentrations and aliquots from each pool were dispensed into individual, daily use containers. It was noted in the laboratory notebook that during the dispensing of pool aliquots, concentration #7 and concentration #8 were switched and, as a result, the concentration of all #7 pools were adjusted to that of pool # 8 and vice versa. (b) (4) acknowledges that documentation of the suspected error during the dispensing of aliquots was not recorded contemporaneously when the error occurred leading to some question regarding the true identity of calibrators #7 and #8. In the absence of a contemporaneous observation and acknowledgement of the suspected labeling error, all calibrators at concentrations #7 and #8 should have been either discarded and remade or, alternatively, the concentrations could have been rejected from the otherwise acceptable calibration curves. During the conduct of the inspection, the partial validation data was reprocessed with deletion of all calibrators at concentrations #7 and #8 (attached). All partial validation data remained within acceptance limits. (b) (4) is confident that the data supported the intent of the partial validation to verify proper assay performance on the Sciex 3000. (b) (4) will modify its SOPs by July 2011 to explicitly prohibit the re-identification of calibration standards and/or quality control samples due to a labeling error unless the error is noted and recorded at the time of preparation.

2) Failure to document error investigations completely and promptly, regarding calibrators #7 and #8 in the Sumatriptan method validation experiments under projects UOJ4 and UOJ5.

Response:

(b) (4) acknowledges that the suspected labeling error was not recorded and investigated contemporaneously. Without the prompt recording of the error, the true identity of calibrators at concentrations #7 and #8 was uncertain. In April 2005, (b) (4) implemented SOP LP-BA-024, Laboratory Investigations. The UOJ4 experiments were conducted in June 2004 and September 2004, prior to implementation of the investigation SOP. Currently, investigations conducted to evaluate suspected errors or anomalous data would be performed as detailed in the current SOP.

Response approved by:

(b) (4)

(b) (4)

Date

(b) (4)

Attachment 1

Method validation data from runs 1UOJ4-B and 2UOJ4-A were reprocessed as runs 1UOJ9-B and 2UOJ9-A with calibrators 7 and 8 deleted. The resulting data are included in this attachment.

Attachment 1. Regression Equations and Correlation Coefficients for Sumatriptan

Regression Equations v3.00

sumatriptan

Final Data - Report Number 1921653

Run ID	Line Equation	R
1UOJ9-B	$Y = 6.445730E-04 + 5.205444E-02 * X$	0.9998
2UOJ9-A	$Y = 1.905793E-03 + 5.158749E-02 * X$	0.9998
	Average Correlation Coefficient	0.9998
Regression Method	Linear Regression, $y = mx + b$, weighted (1/conc)	

Attachment 1. Average Back-calculated Calibration Standards

Statistics Summary v3.08

Report 1921655

Average back calculated calibration standards

sumatriptan

Run ID	CAL 1 (ng/mL)	CAL 2 (ng/mL)	CAL 3 (ng/mL)	CAL 4 (ng/mL)	CAL 5 (ng/mL)	CAL 6 (ng/mL)	CAL 7 (ng/mL)	CAL 8 (ng/mL)	CAL 9 (ng/mL)
1UOJ9-B	0.170	0.513	1.03	2.56	5.09	9.87	X	X	97.9
	0.194	0.503	1.05	2.57	5.00	10.1	X	X	102
2UOJ9-A	0.184	0.474	1.00	2.46	5.08	10.1	X	X	101
	0.190	0.493	1.07	2.68	5.10	10.3	X	X	98.1
N	4	4	4	4	4	4	0	0	4
Theoretical Concentration	0.200	0.500	1.00	2.50	5.00	10.0	25.0	50.0	100
Mean	0.184	0.496	1.04	2.57	5.06	10.1	NC	NC	99.7
S.D.	0.0104	0.0168	0.0263	0.0910	0.0419	0.174	NC	NC	2.07
%C.V.	5.64	3.38	2.53	3.54	0.826	1.72	NC	NC	2.07
% Difference from Theoretical	-7.83	-0.864	3.84	2.75	1.30	1.06	NC	NC	-0.258

LEGEND:

NC Not calculated

X Standard identity cannot be determined

Attachment 1. Intra-assay Precision and Accuracy for Sumatriptan (1UOJ9-B)

Statistics Summary v3.08
Report 1921681
Intra-Assay precision and accuracy
sumatriptan

Run ID	QC 1 (ng/mL)	QC 2 (ng/mL)	QC 3 (ng/mL)
1UOJ9-B	0.487	7.43	76.2
	0.492	7.57	74.5
	0.486	7.74	75.7
	0.495	7.69	76.0
	0.501	7.63	73.8
	0.502	7.58	74.3
N	6	6	6
Theoretical Concentration	0.500	7.50	75.0
Mean	0.494	7.61	75.1
S.D.	0.00704	0.109	0.997
%C.V.	1.43	1.43	1.33
% Difference from Theoretical	-1.24	1.40	0.114
Low Limit	0.425	6.38	63.8
High Limit	0.575	8.63	86.3

Attachment 1. Intra-assay Precision and Accuracy for Sumatriptan (2UOJ9-B)

Statistics Summary v3.08
Report 1921682
Intra-Assay precision and accuracy
sumatriptan

Run ID	QC 1 (ng/mL)	QC 2 (ng/mL)	QC 3 (ng/mL)
2UOJ9-A	0.487	7.41	76.4
	0.507	7.77	76.7
	0.479	7.53	77.1
	0.497	7.61	76.2
	0.476	7.62	77.4
	0.473	7.50	75.9
N	6	6	6
Theoretical Concentration	0.500	7.50	75.0
Mean	0.487	7.57	76.6
S.D.	0.0130	0.122	0.562
%C.V.	2.67	1.61	0.733
% Difference from Theoretical	-2.68	0.995	2.15
Low Limit	0.425	6.38	63.8
High Limit	0.575	8.63	86.3

Attachment 1. Inter-assay Precision and Accuracy for Sumatriptan

Statistics Summary v3.08
Report 1921684
Inter-Assay precision and accuracy
sumatriptan

Run ID	QC 1 (ng/mL)	QC 2 (ng/mL)	QC 3 (ng/mL)
1UOJ9-B	0.487	7.43	76.2
	0.492	7.57	74.5
	0.486	7.74	75.7
	0.495	7.69	76.0
	0.501	7.63	73.8
	0.502	7.58	74.3
2UOJ9-A	0.487	7.41	76.4
	0.507	7.77	76.7
	0.479	7.53	77.1
	0.497	7.61	76.2
	0.476	7.62	77.4
	0.473	7.50	75.9
N	12	12	12
Theoretical Concentration	0.500	7.50	75.0
Mean	0.490	7.59	75.8
S.D.	0.0106	0.112	1.11
%C.V.	2.17	1.47	1.46
% Difference from Theoretical	-1.96	1.20	1.13
Low Limit	0.425	6.38	63.8
High Limit	0.575	8.63	86.3

Attachment 1. Parallelism Precision and Accuracy for Sumatriptan

Statistics Summary v3.08
Report 1921688
Intra-Assay precision and accuracy
sumatriptan

Run ID	QC 4 Dil 5 (ng/mL)
2UOJ9-A	251
	250
	266
	262
	262
	255
N	6
Theoretical Concentration	250
Mean	258
S.D.	6.84
%C.V.	2.65
% Difference from Theoretical	3.05
Low Limit	213
High Limit	288

Attachment 1. Fortified Specificity Samples for Sumatriptan

Statistics Summary v3.08
 Report 1921685
 Limits / Levels for SPF
 sumatriptan

Run ID	SPF 1 (ng/mL)	SPF 2 (ng/mL)	SPF 3 (ng/mL)	SPF 4 (ng/mL)	SPF 5 (ng/mL)	SPF 6 (ng/mL)
1UOJ9-B	0.476 0.489 0.501	0.494 0.496 0.460	0.492 0.498 0.478	0.482 0.484 0.485	0.485 0.505 0.488	0.467 0.479 0.481
N	3	3	3	3	3	3
Theoretical Concentration	0.500	0.500	0.500	0.500	0.500	0.500
Mean	0.489	0.483	0.490	0.484	0.493	0.475
S.D.	0.0125	0.0205	0.0105	0.00163	0.0109	0.00771
%C.V.	2.56	4.23	2.14	0.337	2.20	1.62
% Difference from Theoretical	-2.23	-3.36	-2.08	-3.29	-1.41	-4.90
Low Limit	0.425	0.425	0.425	0.425	0.425	0.425
High Limit	0.575	0.575	0.575	0.575	0.575	0.575

Specificity samples, fortified with sumatriptan at the low-concentration quality control level (nominally 0.500 ng/mL), were prepared from six individual human plasma lots and analyzed to evaluate potential matrix suppression effects.

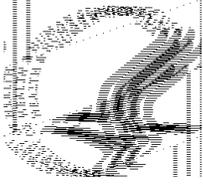
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHARLES R BONAPACE
06/27/2011

 (b) (4)
06/28/2011

MARTIN K YAU
06/28/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Tel 301-769-2110
FAX 301-796-9895

M E M O R A N D U M

Date: 6/3/11

From: Snezana Trajkovic, MD, Medical Officer, DDDP

Through: David Kettl, MD, Clinical Team Leader, DDDP
Susan Walker, MD, Division Director, DDDP

To: Eric Bastings, MD, Deputy Division Director, DNP
Nushin F. Todd, MD, Medical Officer, DNP

CC: Barbara Gould, CPMS, DDDP
Lana Y. Chen, Regulatory Project Manager, DNP
Mathew White, Regulatory Project Manager, DDDP

Re: DDDP Consult # 1319

Division of Neurology Products requested a consult: "Please evaluate hypersensitivity testing" related to Zelrix (Sumatriptan Iontophoretic Transdermal System, NDA (20-2278).

Materials Reviewed: Trial NP 101-008 and Trial NP 101-009

Conclusion:

Based on data from Trial NP 101-008 and Trial NP 101-009, Sumatriptan Iontophoretic Transdermal System has high irritation potential and is sensitizing. No cases of systemic hypersensitivity were reported during the conduct of Trials 101-008 and 101-009. Both trials had open label design, and therefore it is not possible to elucidate if the device or the drug component, or both, of this combination product, is responsible for the observed irritation and sensitization. The potential for sensitization reactions are adequately

addressed in proposed product labeling. The potential for irritation reactions should be further addressed in labeling.

Background:

Sumatriptan is a serotonin receptor agonist indicated for the acute treatment of migraine attacks. In the U.S. sumatriptan is currently available in three formulations – oral tablets, subcutaneous injection, and nasal spray. Sumatriptan was originally approved as Imitrex[®] injection on 12/28/1992.

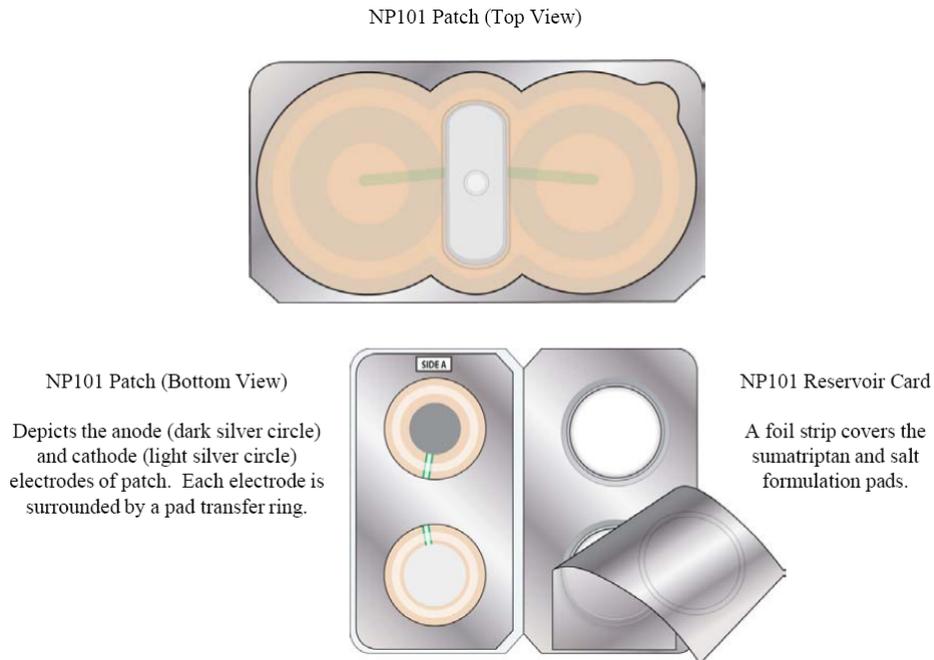
Zelrix[™], Sumatriptan Iontophoretic Transdermal System is a thin, disposable, single-use patch with a self-contained electronic controller and a battery power source designed to deliver sumatriptan transdermally.

Sumatriptan Iontophoretic Transdermal System uses a very mild electrical field which is purported to propel molecules across the skin and into underlying tissue. Power is provided by incorporated lithium ^(b)₍₄₎ batteries designed to deliver a fixed, consistent charge to facilitate absorption through the skin.

Sumatriptan Iontophoretic Transdermal System employs the use of two electrodes with nonwoven pads placed on top of each electrode with one containing the drug formulation (anode), and the other containing a salt formulation (cathode). Application of a low electrical potential across the electrodes is proposed to result in the movement of ionized drug away from the electrode, through the skin, and into the tissue. The quantity of drug transported into the skin is proportional to the total current delivered and is dependent upon a number of criteria, including the molecular weight of the drug ion, drug concentration, and buffer concentration. During iontophoresis there is no mechanical penetration or disruption of the skin.

Figure 1 depicts Sumatriptan Iontophoretic Transdermal Patch.

Figure 1: NP101 Sumatriptan Iontophoretic Transdermal Patch



Source: Sponsor's submission

End of the Phase 2 meeting was held on 11/24/09. DDDP informed the sponsor of need to conduct dermal safety evaluation prior to approval. This was communicated to the sponsor in the letter on 3/5/10.

DNP requested consultation from DDDP as a follow up to this recommendation and after the sponsor provided information from ongoing long term Phase 3 trials (101-008 and 101-009), where NP101 was shown to be sensitizing. The sponsor requested a waiver for the need to conduct a dermal sensitization study. Considering that 21 day sensitization /irritation studies with the active drug containing patch cannot be safely performed (due to significant increase of drug exposure), DDDP provided the following recommendation to the sponsor on July 13, 2010:

“You have submitted studies that are not adequate provocative dermal safety evaluations. However, since you have acknowledged that your product is sensitizing in actual use trials, the information collected during the open label phase 3 trials has the potential to be sufficient for product labeling”.

Review

Trial NP 101-008

Trial Title

An Open-Label Study To Evaluate the Safety of NP101, a Sumatriptan Iontophoretic Transdermal Patch, in the Treatment of Acute Migraine over 12 Months.

Trial objective

The primary objective of this study was to evaluate the safety of long-term treatment with NP101.

Study population:

Subjects previously enrolled in Study NP101-007, who continued to be in good health and received treatment with the study patch under study NP101-007, were eligible for enrollment into this study.

Inclusion Criteria

Subjects were to meet all of the following inclusion criteria to enter the study:

1. Subject was previously enrolled in study NP101-007 and treated (patch activation) a qualifying migraine headache.
2. Subject was judged to be in good health, based upon the results of a medical history, physical examination, vital signs, and ECG. Subject did not have any clinically significant abnormal vital signs or ECG parameters. ECG was to be done at enrollment for NP101-008 unless the ECG for the Final Visit of study NP101-007 was conducted within 30 days.
3. Female subjects of childbearing potential (not surgically sterile or 2 years post menopausal) must have had a negative pregnancy test at enrollment.

Exclusion Criteria

Subjects were to be excluded from study participation for the following reasons:

1. Subject had less than two potential skin application sites.
2. Subject had clinically significant abnormal vital signs or ECG parameters or had an adverse event while participating in NP101-007 that precluded the continued treatment with the NP101 patch.
3. Subject had changes in their medical history or medication use that precluded their use of sumatriptan as per the approved Imitrex® product package insert or their safe use of NP101 as per the NP101 Investigator's Brochure.
4. Subject had or planned to start, stop, change treatment or dose of any of the following

within 3 months prior to the subject's study Enrollment date and through the Final Visit: anxiolytics, lithium and other mood stabilizers such as valproate, carbamazepine or lamotrigine, hypnotics or antipsychotics.

5. Subject had taken non-triptan serotonergic drugs including selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressants (TCAs), monoamine oxidase inhibitor (MAOI) or preparations containing St. John's Wort within 1 month prior to enrollment and/or was planning to start any of these medications during the study (through Final Visit).

6. Female subjects who were pregnant, breast feeding, or of childbearing potential, and were not using or were unwilling to use an effective form of contraception during the study and for a period of 30 days following Final Visit. Acceptable methods of contraception included barrier method with spermicide, intrauterine device (IUD), steroidal contraceptive (oral, transdermal, implanted or injected) or abstinence. If the exclusive male partner was surgically sterile, this was acceptable.

7. Subject had participated in a clinical study within 30 days of enrollment (excluding NP101-007) or was planning to participate in another clinical study for the duration of NP101-008.

Trial design and procedures

This was an open-label, multicenter, phase 3 trial. One hundred eighty-three (183) subjects applied at least one NP101 patch in this study; a total of 2089 patches were applied and activated.

Subjects were treated for up to 12 months during which they were allowed to apply a maximum of six patches within a 30-day period. Subjects were not to apply more than two NP101 patches within a 24-hour period.

Patch application sites for subjects included right and left upper arms and right and left thighs. Patches were worn for four hours. A patch was not to be applied to a previous application site until the site remained erythema free for 72 hours.

The subject was to perform a self examination of the patch application site four hours after patch activation (within 10 minutes of patch removal) and again at 6, 12, and 24 hours.

Subject's skin irritation was rated using the following 5-point scale presented in Table 1:

Table 1: Subject Skin Self-examination Irritation Score

Score	Definition
0	No redness;
1	Minimal skin redness;
2	Moderate skin redness with sharp borders;
3	Intense skin redness with or without swelling;
4	Intense skin redness with blisters or broken skin

Source: Sponsor's submission

If the skin irritation score was not 0 at 24 hours, a self examination of the patch application site was to be completed daily until the score returned to 0. The subject recorded the skin irritation score in the Migraine Study Diary. A score of 3 or 4 was to be reported to the principal investigator or qualified designee and the subject was to be seen within 24 hours.

For subjects who had a skin irritation score of 3 or 4 at any visit, the principal investigator or qualified designee evaluated the subject and at the principal investigators discretion but, at minimum, a **Unscheduled Follow-up Visit** was to occur every 7 days (\pm 2 days) to complete another skin irritation examination with continued weekly follow-up until the skin irritation score was zero (0).

Any skin irritation score of 4, or if the event was deemed to be ACD (delayed hypersensitivity reaction) as assessed by the principal investigator or qualified designee, was to be reported as an expedited adverse event. Subjects who met all criteria under **Definition for Putative Cases of Allergic Contact Dermatitis (ACD)**, as outlined below, were to be offered a referral for testing to determine whether they had developed topical sensitivity to sumatriptan.

If a subject reported a worsening of skin irritation after a period of improvement or whose skin irritation score significantly worsened on subsequent patch applications, the principal investigator or qualified designee was to assess whether the event was indicative of allergic contact dermatitis (ACD), a delayed hypersensitivity reaction.

“Definition for Putative Cases of Allergic Contact Dermatitis (ACD)

Subjects who meet all criteria under **Clinical Course, Morphology and Symptoms** should be referred for testing to determine whether they have developed topical sensitivity to sumatriptan.

Clinical Course:

- Sensitizing exposure required: Subject could have been previously exposed by taking subcutaneous sumatriptan or by transdermally administered sumatriptan through iontophoretic (NP101) use.

- Clinical lesions (see Morphology) appear after subsequent challenge(s) with antigen (i.e. sumatriptan). Lesions usually appear 24-72 hours after last exposure (but may develop as early as 5 hours or as late as 7 days after exposure).
- Clinical course characterized by crescendo phenomenon (clinical course / appearance worsens over time) followed by slower resolution.

Morphology:

- Most common: erythematous plaques (with or without edema) and / or erythematous-vesicular or erythematous-bullous eruptions, sometimes evolving to oozing dermatitis.
 - a. Intense vesiculation increases suspicion of ACD. Pustules, necrosis, or ulceration rarely seen.
- Lesions are stronger in the contact area (but limits are usually ill-defined).
 - b. Dissemination with distant lesions may occur.

Symptoms:

- Pruritus

All subjects who had a skin irritation score of ≥ 1 at the Final Visit were asked to continue to complete their Migraine Study Diary (recording daily assessments until the skin irritation score returns to zero) and to return for weekly Unscheduled Follow-up Visits until the principal investigator or qualified designee rated the skin irritation score a zero.

Investigator Skin Irritation Examinations

At Months 1, 2, 3, 6, 9, 12 (or Final Visit) and at all Unscheduled Follow-up Visits, the principal investigator or qualified designee examined all subject patch placement sites and scored the site with the worst skin irritation using the following scoring system presented in Table 2.

Table 2: Investigator’s Skin Irritation Score

Score	Definition
0	No erythema
1	Minimal erythema
2	Moderate erythema with sharp defined borders
3	Intense erythema with or without edema
4 ^a	Intense erythema with edema and blistering/erosion

^a... A score of 4 required at all times the presence of intense erythema. If a blister or skin abrasion was noted on examination but there was no intense erythema, a lower score, commensurate with the level of the erythema, should have been assigned

Source: Sponsor’s submission

Guidelines for applying and wearing the study patch were as follow:

- The patch was not to be applied over skin that was irritated. Skin was to be relatively hair free without scars or tattoos. The study patch was not to be applied over scratches or abrasions.
- The patch must lie flat over the skin for the patch to function properly. If the patch did not lie flat, it was to be removed.
- Subjects were to keep the patch dry and were not to bathe, shower or swim while wearing the study patch.
- The subject had four patch placement sites to choose from; right upper arm, right thigh, left upper arm, left thigh.
- If the subject chose to apply the patch to the right or left thigh, they were to be in a standing position when applying the patch.
- Subjects may have applied the NP101 study patch as a rescue medication if relief was not achieved two hours after initial patch activation (for pain scores of 1, 2 or 3). The patches were not to overlap each other and a patch was only applied to a previous application site if the self skin irritation score had remained 0 for at least 72 hours following patch removal.
- If the formulation from the under the patch leaked onto the subject's arm and/or thigh/leg, the subject was to clean the affected area with soap and water.
- It was to be clearly understood by the subject during their instruction on patch application that both medication pads must lie flat over the electrodes before applying and activating the NP101 patch, and that the consequence of not having the pads directly over the electrodes during patch application and activation may be an intense skin reaction with pronounced redness, blisters and or broken skin.
- The subject was not to use any ergot or other triptan medications 24 hours before or after any NP101 patch activation.
- The subject was not to use any analgesic or antiemetic medication 8 hours prior to initial NP101 patch activation.
- The subject was not to use any medications to treat their initial acute migraine symptoms (i.e. pain, nausea, photophobia or phonophobia) within the first two hours after the initial NP101 patch activation.
- When treating an initial acute qualifying migraine, the subject was to rate the severity of their migraine using the Diary Headache Pain Severity scores. Subjects should not have used the NP101 study patch within 24 hours prior to treatment of the initial acute migraine attack.
- No more than two NP101 patches were to be applied in a 24-hour period.
- The NP101 transdermal iontophoretic patch was not to be applied or used during an MRI scan, and if already being used, the NP101 transdermal iontophoretic patch was to be removed.

There were seven scheduled study visits: Study Visit 1 (Enrollment), Visit 2 (Month 1), Visit 3 (Month 2), Visit 4 (Month 3), Visit 5 (Month 6), Visit 6 (Month 9) and Visit 7 (Month 12 or Final Visit). In addition, subjects returned to the investigative site as needed

to turn in and obtain additional study patches (Patch Dispensing Visits), or when required for additional skin irritation assessments or follow-up (Unscheduled Visits).

Results of Trial NP 101-008

A total of 2089 patches were used by 183 subjects over the 12-month period of study. More than half of all treated subjects (55.7%) used at least 6 patches during the study, and 30.6% used at least 12 patches. A total of 76 subjects met the definition of a 6-month completer (subjects who were enrolled for at least 166 days and applied at least 6 patches within the first 180 days of enrollment) and 51 subjects met the definition of a 12-month completer (6-month completers who were enrolled for at least 346 days and applied at least 9 patches within the first 360 days of enrollment).

Skin irritation evaluation

Subject's skin irritation evaluation results

Subjects performed their own examination of the patch site at 4, 6, 12, and 24 hours post patch activation, and daily thereafter until resolution. If subject's irritation score was reported to be 3 or 4, principal investigator or qualified designee would evaluate the patient within 24 hour of report.

At the time of patch removal (4 hours post patch activation), subject self-examination skin irritation scores indicated no redness or minimal redness for 38.2% of all patches scored at that time point during the study, moderate redness for 54.0%, and intense redness for 7.8%.

By 24 hours after patch application, 65.4% of all patch applications had minimal or no redness, while 31.2% were scored as having moderate redness, 45 patch application sites (2.3%) had a score of 3 (intense redness with or without swelling), and 20 (1.0%) had a score of 4 (intense redness with blisters or broken skin).

By 6 days post-application, six application sites still had a score of 3 and seven had a score of 4.

By 11 days post-application, there were two patch sites with a score of 3 (none with a score of 4).

By 16 days post-application, there were no scores of 3 or 4. The mean time to resolution of erythema (based on a total of 1871 patches for which complete data were available) was 3.5 days and the median time to resolution of erythema was 2.0 days.

Results from subject's skin irritation evaluation revealed that NP101 transdermal iontophoretic patch was irritating (24 hours post patch application, over 30% of subjects had moderate to intense redness at the application site).

Subject's self-examination skin irritation scores for the first 24 hours are reported in Table 3.

Table 3: Subject's Self-examination Skin Irritation Scores

Skin Assessment Scores	Time Point Post Patch Application (N=183)			
	4 Hours	6 Hours	12 Hours	24 Hours
Number of patches scored	1920	2019	1950	1917
Distribution, n (%) ^a				
No redness	200 (10.4)	366 (18.1)	515 (26.4)	792 (41.3)
Minimal redness	534 (27.8)	562 (27.8)	565 (29.0)	462 (24.1)
Moderate redness	1037 (54.0)	959 (47.5)	788 (40.4)	598 (31.2)
Intense redness with or without swelling	139 (7.2)	125 (6.2)	71 (3.6)	45 (2.3)
Intense redness with blisters or broken skin	10 (0.5)	7 (0.3)	11 (0.6)	20 (1.0)
Missing ^b	7	2	3	5
Mean (SD)	1.6 (0.79)	1.4 (0.87)	1.2 (0.90)	1.0 (0.96)
Median	2.0	2.0	1.0	1.0
Minimum, Maximum	0, 4	0, 4	0, 4	0, 4

^a The denominator is the total number of patches with a score at the respective time point.

^b Missing is not included in the denominator.

Source: Sponsor's submission

When subject's skin irritation scores at 24-hours, by month, were evaluated the following results were obtained:

From Month 1 to Month 2, there appeared to be some increase in the percentage of subjects with 24-hour skin irritation scores of 3 or 4 along with an increase in mean score from 1.0 to 1.3; however, the difference in the number of patch applications assessed (515 and 157, respectively) makes it difficult to draw conclusions from these data.

For Month 3 through Month 11, when the number of patches scored per month was fairly stable, there was no evidence of an increase in skin irritation over time, with mean scores ranging from 0.7 to 1.2.

Summary of subject skin irritation assessment at 24 hours after patch activation by study month are presented in Table 4.

Table 4: Summary of Subject Skin Irritation Assessment at 24 Hours after Patch Activation by Study Month (Safety Population)

	Subject Skin Irritation Scores at 24 Hours after Patch Activation (N=183)											
	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Number scored	515	157	117	112	143	140	132	108	141	129	135	87
Distribution, % ^a												
Score = 0	34.6	32.5	40.2	40.2	37.8	37.9	50.8	50.0	45.4	52.7	48.1	51.7
Score = 1	30.5	22.9	25.6	17.0	22.4	22.1	12.1	23.1	23.4	24.8	24.4	20.7
Score = 2	32.2	33.8	29.1	33.0	36.4	37.1	34.1	26.9	30.5	21.7	25.9	27.6
Score = 3	1.6	7.6	3.4	4.5	3.5	2.9	3.0	0	0.7	0.8	0.7	0
Score = 4	1.2	3.2	1.7	5.4	0	0	0	0	0	0	0.7	0
Mean	1.0	1.3	1.0	1.2	1.1	1.1	0.9	0.8	0.9	0.7	0.8	0.8
SD	0.91	1.09	1.00	1.17	0.94	0.93	0.98	0.85	0.88	0.83	0.90	0.86
Median	1.0	1.0	1.0	1.0	1.0	1.0	0.0	0.5	1.0	0.0	1.0	0.0
Min, Max	0, 4	0, 4	0, 4	0, 4	0, 3	0, 3	0, 3	0, 2	0, 3	0, 3	0, 4	0, 2

^a Percentage based on the total number of patches with a 24-hour post patch activation score at the respective study month.

0 = no redness; 1 = minimal redness; 2 = moderate redness; 3 = intense redness with or without swelling; 4 = intense redness with blisters or broken skin; SD = standard deviation.

Source: Sponsor's submission

Investigator's Skin Irritation Assessment

At each visit, the Investigator or other qualified personnel examined all patch placement sites and scored the site with the worst skin irritation score using the scale shown in Table 5.

The majority of subjects (>74%) had no erythema at patch application sites. Except for one subject at Month 6, and four subjects at Month 12/Final Visit, the remaining subjects evaluated at each visit had minimal or moderate erythema at the site of worst irritation. There were two subjects with skin irritation scores rated as 4 by the Investigator at the Month 12/End of Study visit and three other subjects with scores of 4 at Unscheduled Visits. All of these subjects were discontinued from study due to AE (application site hypersensitivity /allergic contact dermatitis).

Table 5: Investigator Highest Skin Assessment by Study Month

Visit	Assessment^a	NP101 N=183 (%)
Month 1	No erythema	109 (74.7)
	Minimal erythema	28 (19.2)
	Moderate erythema	9 (6.2)
	Intense erythema /with or without edema	0
	Intense erythema /with edema and blistering	0
	Missing	37
Month 2	No erythema	108 (81.8)
	Minimal erythema	19 (14.4)
	Moderate erythema	5 (3.8)
	Intense erythema/with or without edema	0
	Intense erythema /with edema and blistering	0
	Missing	51
Month 3	No erythema	80 (85.1)
	Minimal erythema	12 (12.8)
	Moderate erythema	2 (2.1)
	Intense erythema/with or without edema	0
	Intense erythema /with edema and blistering	0
	Missing	89
Month 6	No erythema	57 (82.6)
	Minimal erythema	8 (11.6)
	Moderate erythema	3 (4.3)
	Intense erythema/with or without edema	1 (1.4)
	Intense erythema /with edema and blistering	0
	Missing	114

Table 5: Investigator Highest Skin Assessment by Study Month (continued)

Visit	Assessment	NP101 N=183 (%)
Month 9	No erythema	59 (92.2)
	Minimal erythema	5 (7.8)
	Moderate erythema	0
	Intense erythema/with or without edema	0
	Intense erythema /with edema and blistering	0
	Missing	119
Month 12/ End of Study	No erythema	136 (84.5)
	Minimal erythema	13 (8.1)
	Moderate erythema	8 (5.0)
	Intense erythema/with or without edema	2 (1.2)
	Intense erythema /with edema and blistering	2 (1.2)
	Missing	22

^a Missing is not included in the denominator.

Source: Sponsor's submission

Investigator's assessment of irritation revealed that NP101 transdermal iontophoretic patch was not as irritating (more than 90% of subjects had no or minimal erythema) in comparison to subject's assessment (24 hours post patch application, over 30% of subjects had moderate to intense redness) at the application sites. The disparity of subject's and investigator's skin irritation assessments were due to difference of timing of assessments (subject's assessment was performed 4, 6, 12, and 24 hours post patch activation while investigator's assessment was performed during regular office visits irrespective of time of patch application).

Allergenicity Evaluation

A total of 14 cases of allergic contact dermatitis (ACD) were identified by medical specialist review including those with a recorded AE of application site hypersensitivity /ACD. Of these, six cases fully met the putative ACD diagnosis criteria utilized by the medical and dermatology review group and were deemed to be "probable"; the remaining 8 cases were deemed "possible". The overall rate of ACD with NP101 in subjects with at least two patch applications was 3.7% (6/164) when "probable" cases were considered, and 8.5% (14/164) when "possible" and "probable" cases were included.

Rates of ACD appeared to be decreasing after use of nine or more patches. No ACD cases were observed after the use of 12 or more patches. In the opinion of this reviewer the reason for decrease in number of ACD with continuous patch use is due to discontinuation of subjects who developed ACD with patch use at earlier time points during the trial.

Adverse events

The most frequently reported AEs, experienced by 45% of all treated subjects, were in System Organ Class (SOC) of “Application site conditions”, and at the Proffered Term (PT) application site pruritus (21.9%), application site pain (21.3%), application site hypersensitivity (ACD; 6.0%), application site exfoliation (4.9%), application site reaction (4.9%), application site paraesthesia (4.4%), and application site vesicles (3.8%).

Discontinuations due to adverse events

Twenty-five (25) subjects (13.7%) discontinued study due to adverse events. One subject (0.5%) discontinued due to nausea; one subject discontinued due to dizziness; and 23 subjects (12.6%) discontinued due to application site conditions.

The “APPLICATION SITE CONDITIONS” [25 (13.7%)] leading to discontinuation were:

- Application site hypersensitivity (8, 4.4%);
- Application site pain (6, 3.3%);
- Application site discoloration (2, 1.1%);
- Application site pruritus (3, 1.6%);
- Application site anesthesia, bruising, discomfort, reaction, and vesicles (1 subject each, 0.5%).

Two serious adverse events were reported during the study: severe vertigo considered unrelated to study drug, and severe dehydration considered unrelated to study drug.

Trial NP 101-009

Trial Title

An Open-Label Study To Evaluate the Safety of NP101, a Sumatriptan Iontophoretic Transdermal Patch, in the Treatment of Acute Migraine over 12 Months

Trial objective

The primary objective of this study was to evaluate the safety of long-term treatment with NP101.

Trial design and procedure

This was an open-label design to assess the long term safety of NP101 (sumatriptan iontophoretic transdermal patch).

Study population

Please see Inclusion Criteria and Exclusion Criteria for Trial NP 101-008

Trial design and procedures

Please see trial design and procedures for Trial NP 101-008

Results of Trial NP 101-009

Subject's Self-examination Skin Irritation Scores

Subjects performed their own examination of the patch site at 4, 6, 12, and 24 hours post patch activation, and daily thereafter until resolution, and scored skin irritation using the scale shown in Table 6.

Four hundred seventy nine (479) subjects applied at least one NP101 patch in this study; a total of 5562 patches were applied and activated. 63.5% of subjects used at least 6 patches during the study, and 41.3% used at least 12 patches.

At the time of patch removal (4 hours post patch activation), subject self-examination skin irritation scores indicated no redness or minimal redness for 49.3% of all patches scored at that time point during the study, moderate redness for 45.3%, and intense redness with or without swelling for 5.1% and intense redness with blisters or broken skin in 0.4%.

By 24 hours after patch application, 77.7% of all patch applications had minimal or no redness, while 19.8% were scored as having moderate redness, 2.1% had a score of 3 (intense redness with or without swelling), and 0.4% had a score of 4 (intense redness with blisters or broken skin).

By 16 days post-application, there were 2 scores of 3 and one score of 4. The mean time to complete resolution of erythema (based on a total of 5562 patches for which complete data were available) was 2.7 days and the median time to resolution of erythema was 1.0 day.

The results from subject's skin irritation evaluation revealed that NP101 transdermal iontophoretic patch was irritating (24 hours post patch application, over 20% of subjects had moderate to intense redness of application sites).

A summary of subject skin irritation assessments at patch removal (4 hours), 6 hours, 12 hours and 24 hours post patch activation is shown in Table 8.

Table 8: Summary of Subject Skin Assessment at Each Time Point within 24 hours after Patch Application (Safety Population)

Skin Assessment Scores	Time Point Post Patch Application (N=479)			
	4 Hours	6 Hours	12 Hours	24 Hours
Number of patches scored	5458	5438	5390	5342
Distribution, n (%) ^a				
No redness	1084 (19.9)	1496 (27.5)	2086 (38.7)	3091 (57.9)
Minimal redness	1605 (29.4)	1607 (29.6)	1645 (30.5)	1059 (19.8)
Moderate redness	2473 (45.3)	2108 (38.8)	1481 (27.5)	1060 (19.8)
Intense redness with or without swelling	276 (5.1)	208 (3.8)	161 (3.0)	113 (2.1)
Intense redness with blisters or broken skin	20 (0.4)	19 (0.3)	17 (10.3)	19 (0.4)
Missing ^b	3	7	7	7
Mean (SD)	1.4 (0.87)	1.2 (0.90)	1.0 (0.90)	0.7 (0.89)
Median	2.0	1.0	1.0	0.0
Minimum, Maximum	0, 4	0, 4	0, 4	0, 4

^a The denominator is the total number of patches with a score at the respective time point.

^b Missing is not included in the denominator.

Source: Sponsor's submission

When subject skin irritation assessment scores by study month were analyzed by subset according to cumulative patch usage (above or below the median), there were no overall trends to suggest that subjects whose cumulative patch usage was above the median experienced any greater skin irritation than did subjects whose cumulative patch usage was equal to or below the median.

From Month 1 through Month 7, when more than 100 patches per month were used, the percentage of patches with 24-hour skin irritation scores of 3 or 4 was similar over time with mean scores ranging from 0.5 to 0.7. Subject skin irritation scores on subsequent days post patch application also did not show any trends towards an increase in skin irritation with successive patch usage.

The mean time to complete resolution of erythema at patch application sites was 2.7 days and the median time to resolution of erythema was 1.0 day.

Summary of skin irritation assessment at 24 hours after patch activation by study month are presented in Table 9.

Table 9: Summary of Subject Skin Irritation Assessment at 24 Hours after Patch Activation by Study Month (Safety Population)

	Subject Skin Irritation Scores at 24 Hours after Patch Activation (N=479)											
	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Number scored	1719	826	697	568	547	366	238	222	104	24	25	5
Distribution, % ^a												
Score = 0	53.3	58.8	59.4	62.3	63.8	57.4	61.8	54.1	71.2	33.3	36.0	40.0
Score = 1	25.3	19.0	17.2	15.5	15.9	19.1	15.5	23.4	8.7	8.3	4.0	20.0
Score = 2	18.6	19.4	20.4	20.1	17.6	22.1	21.8	20.3	18.3	58.3	60.0	40.0
Score = 3	2.5	2.2	2.6	1.6	2.6	0.8	0.4	2.3	1.9	0	0	0
Score = 4	0.2	0.6	0.4	0.5	0.2	0.5	0.4	0	0	0	0	0
Mean	0.7	0.7	0.7	0.6	0.6	0.7	0.6	0.7	0.5	1.3	1.2	1.0
SD	0.87	0.90	0.91	0.89	0.88	0.88	0.87	0.87	0.86	0.94	0.97	1.00
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.0	2.0	1.0
Min, Max	0, 4	0, 4	0, 4	0, 4	0, 4	0, 4	0, 4	0, 3	0, 3	0, 2	0, 2	0, 2

^a Percentage based on the total number of patches with a 24-hour post patch activation score at the respective study month.

0 = no redness; 1 = minimal redness; 2 = moderate redness; 3 = intense redness with or without swelling; 4 = intense redness with blisters or broken skin; SD = standard deviation.

Source: Sponsor's submission

Investigator's Skin Irritation Assessment

At each visit, the Investigator or other qualified personnel examined all patch placement sites and scored the site with the worst skin irritation score using the scale shown in Table 1.

There were 15 subjects with skin irritation scores rated as 4 by the Investigator during at least one Study visit. Fourteen of these subjects with AEs led to discontinuation of study drug. Two subjects did not discontinue study due to an AE but were lost to follow-up.

Investigator's assessment of irritation revealed that NP101 transdermal iontophoretic patch was not as irritating (more than 90% of subjects had no or minimal erythema) in comparison to subject's assessment (24 hours post patch application, over 20% of subjects had moderate to intense redness) at the application sites.

The disparity of subject's and investigator's skin irritation assessments were due to difference of timing of assessments (subject's assessment was performed 4, 6, 12, and 24 hours post patch activation while investigator's assessment was performed during regular office visits irrespective of time of patch application).

Allergenicity Evaluation

A total of 30 potential cases of allergic contact dermatitis (ACD) were identified by medical and dermatology ACD expert review. Of these, 12 cases fully met the putative ACD diagnosis criteria utilized by the review group and were deemed to be "probable"; the remaining 18 cases were deemed "possible". The overall rate of putative ACD with NP101 use in subjects with at least two patch applications was 2.7% (12/442) when

“probable” cases were considered and 6.8% (30/442) when “possible” and “probable” cases were included.

Discontinuations

Sixty-two (12.9%) subjects were discontinued due to AEs, primarily patch application site disorders. One subject (0.2%) each discontinued due to supraventricular tachycardia, diarrhea, nausea, herpes zoster, headache, and rash macula-papular. Three subjects (0.6%) discontinued due to depression and 53 subjects (11.1%) discontinued due to application site conditions.

The “APPLICATION SITE CONDITIONS” [62 (12.9%)] leading to discontinuation were:

- Application site hypersensitivity (15, 3.1%)
- Application site pain (15, 3.1%)
- Application site discoloration (5, 1.0%)
- Application site irritation (5, 1.0%)
- Application site pruritus (5, 1.0%)
- Application site reaction (2, 0.4%)
- Application site bruising, burn, induration, paraesthesia, and rash (1 subject each, 0.2%).

Application site hypersensitivity was evaluated as described in “**Definition for Putative Cases of Allergic Contact Dermatitis (ACD)**”.

Adverse Events

The most frequently reported AEs, were in SOC “Application site conditions”, and at PT level were: application site pain (16.3%), application site pruritus (12.7%), application site reaction (6.1%), application site paraesthesia (5.4%), application site dryness (5.0%), application site discoloration (4.0%) and application site hypersensitivity (3.5%).

Seven serious adverse events were reported during the study: nephrolithiasis, headache, back pain, ectopic pregnancy, supraventricular tachycardia, syncope, and atrial fibrillation. None of the events were considered by the investigator to be related to study medication.

Conclusion

Based on data from Trial NP 101-008 and Trial NP 101-009, Zelrix™, Sumatriptan Iontophoretic Transdermal System has significant irritation potential and is sensitizing. No cases of systemic hypersensitivity were reported during the conduct of Trials 101-008 and 101-009. There is no record that any subject required epinephrine or other emergency care for treatment of anaphylaxis. Since both trials

were open label, and no placebo containing patches were evaluated, it is not possible to conclude if device or drug component of this combination product is responsible for irritation and sensitization. Information on sensitization potential was addressed in product labeling. Information on irritation potential of patch product should be addressed adequately in labeling.

The sponsor proposed under section “5. WARNINGS AND PRCAUTIONS” subsection “5.8 (b) (4)” to include systemic hypersensitivity reactions, (anaphylaxis/anaphylactoid) experienced with other sumatriptan products, but not seen with Zelrix, as follows:



The proposed labeling adequately informs health care professional of potential for allergic contact dermatitis and systemic sensitization after exposure to Zelrix, and the possible implications for other dosage forms of sumatriptan.

Inclusion of labeling from other approved products in the sumatriptan class is recommended given the adverse reaction experience related to hypersensitivity from currently marketed sumatriptan products.

Irritation potential of the patch product was addressed in labeling in section “5. WARNINGS AND PRCAUTIONS” subsection “5.11 (b) (4)” as follows:



However, Zelrix may cause irritation even with proper use (not only with improper application) and labeling should adequately inform prescribers of this potential adverse reaction.

APPEARS THIS WAY ON ORIGINAL

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

/s/

SNEZANA TRAJKOVIC
06/17/2011

DAVID L KETTL
06/17/2011

SUSAN J WALKER
06/20/2011

PMA REVIEW MEMORANDUM for OC/OIVD

DATE: May 25, 2011

TO: The Record

THROUGH: Chief, Orthopedic and Physical Medicine Devices
Branch, Division of Enforcement B, Office of
Compliance, CDRH, WO66-36

MEJ 14 July 2011
initials date

FROM: Regulatory Operations Officer, Orthopedic and
Physical Medicine Devices Branch, Division of
Enforcement B, Office of Compliance, CDRH WO66-
3659

SUBJECT: **NDA 202278 – Sumatripan Iontophoretic
Transdermal System / Zelrix – Device QS Review**

LIST ALL SITES: Applicant: **NuPathe, Inc.**

**221 Washington Street
Suite 200
Conshohocken, PA 19428**

**[NOTE: If applicant's
address is also a design
controls or
manufacturing site,
include this site under
the Mfg Site(s): section
below.]**

Mfg Site(s): **NuPathe, Inc.
221 Washington Street
Suite 200
Conshohocken, PA 19428
FEI: not yet established**

Final Release / Design Controls

Requires Inspection? Y N
Site ready for inspection? Y N
N/A
If no, add date site will be ready:

Contract
Manufacturer
Site(s)

(b) (4)

(b) (4)

Requires Inspection? Y N
Site ready for inspection? Y N
N/A
If no, add date site will be ready:

(b) (4)

(b) (4)

Requires Inspection? Y N
Site ready for inspection? Y N
N/A
If no, add date site will be ready:

(b) (4)

(b) (4)

Requires Inspection? Y N
Site ready for inspection? Y N
N/A
If no, add date site will be ready:

DEVICE: Sumatripan Iontophoretic Transdermal System /
Zelrix

OC/OIVD

RECOMMENDATION: *Information inadequate – Send Deficiency Letter.*

INTENDED USE:

Acute treatment of migraine attacks, with or without aura, in adults.

DEVICE DESCRIPTION:

Zelrix™ is a disposable, single-use, co-packaged drug/device combination product that utilizes iontophoretic technology to deliver sumatripan transdermally for the treatment of acute migraine attacks.

Iontophoresis is a non-invasive drug delivery method that uses low electrical current to move ionized drugs across the skin to the underlying tissue and blood vessels.

**INSPECTION HISTORY (MANUFACTURER AND/OR CONTRACT
MANUFACTURER SITE(S)):**

This is an NDA, CDER has lead and should cover this section.

CORRESPONDENCE HISTORY:

The firm was not contacted during this review.

FIRM CONTACT (US ADDRESS ONLY):

Michele A. Roy, RN, MS
NuPathe, Inc,
227 Washington Street,
Suite 200
Conshohocken, PA 19428

SECTION I: DESIGN CONTROL INFORMATION:

Design Control, General, CFR 820.30(a)

The firm provided SOP QS-003: Design Control and Pharmaceutical Development (rev .03) which covers their design control procedures. Initial research and development studies for the device component of NP101 (The Electrode Patch) were performed under a developmental license with (b) (4). On January 1, 2007, the research and development agreement with (b) (4) ended, and the product development

came under the NuPathe's design control program.

The SOP QS-003 procedure covers new product development and product changes. It states that [REDACTED] (b) (4)

The SOP QS-003 procedure discusses responsibilities for design projects, including a [REDACTED] (b) (4)

[REDACTED] It is not clear if this is at all related to validation or verification, but that is reviewed later on in this memo.

The SOP QS-003 procedure also defines the expected 21 CFR 820.30 parts of design control.

The SOP QS—03 procedure describes the processes of [REDACTED] (b) (4)

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.30(a).

Design and Development Planning, 820.30(b)

The firm provided rep-dhf-np101-079.pdf - a development plan in chart form for development of the Zelrix Patch. The form appears to assign responsible resources (as initials). Each part of the design process appears clearly marked and identifiable. Design reviews are noted.

The "device-info-amend-3-14-2011.pdf" document found in Amendment 7 (3/17/11) contains further information to decode the provided development plan. It notes design inputs and sources of the design inputs. It also notes that the [REDACTED] (b) (4)

[REDACTED] (b) (4)

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.30(b).

Design Input, 820.30(c)

The firm provided SOP QS-003: Design Control and Pharmaceutical Development, Section 4.3: Design Input. Form F-QS-008, Design Input/Output and Design Verification was also provided.

DEFICIENCY 1:

You provided SOP QS-003: Design Control and Pharmaceutical Development, Revision .03, in order to satisfy the requirements of 21 CFR 820.30(c), Design Input. In this document, you define Design Inputs and provide the (b) (4)

[REDACTED]

DEFICIENCY 2:

You provided SOP QS-003: Design Control and Pharmaceutical Development, Revision .03, in order to satisfy the requirements of 21 CFR 820.30(c), Design Input. In your submission, you state that this procedure addresses (b) (4)

[REDACTED]

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.30(c).

Design Output, 820.30(d)

The firm provided SOP QS-003: Design Control and Pharmaceutical Development, Section 4.4 – Design Output. The design outputs specific to the E-Patch are described in the "device-info-amend-3-14-2011.pdf" document found in Amendment 7 (3/17/11), Section 1.4. The firm lists (b) (4)

[REDACTED]

(b) (4)

DEFICIENCY 3

You provided SOP QS-003: Design Control and Pharmaceutical Development, Revision .03, in order to satisfy the requirements of 21 CFR 820.30(d), Design Output. In this procedure, you describe

(b) (4)

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.30(d).

Design Review, 820.30(e)

The firm provided SOP QS-003: Design Control and Pharmaceutical Development, Section 4.5 – Design Reviews. The design review information specific to the E-Patch is described in the “device-info-amend-3-14-2011.pdf” document found in Amendment 7 (3/17/11), Section 1.5. The procedures state

(b) (4)

(b) (4)

DEFICIENCY 4

You provided SOP QS-003: Design Control and Pharmaceutical Development, Revision .03, and forms F-QS-010, Design Review Checklist, and F-QS-009, Design Documentation in order to satisfy the requirements of 21 CFR 820.30(e), Design Review. SOP QS-003, section 4.5 explains that the Project Team will

[REDACTED] (b) (4)

Please provide a revised Design Control procedure and/or design review checklist that clarifies the responsibility of QA, or changes the signature authority of the checklist to an individual identified as not having responsibility in the Design Control procedure.

DEFICIENCY 5

You provided SOP QS-003: Design Control and Pharmaceutical Development, Revision .03, and forms F-QS-010, Design Review Checklist, and F-QS-009, Design Documentation in order to satisfy the requirements of 21 CFR 820.30(e), Design Review. In form F-QS-010, Design Review Checklist, you state that (b) (4)

[REDACTED]

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.30(e).

Design Verification, 820.30(f)

The firm provided SOP QS-003: Design Control and Pharmaceutical Development, Section 4.6 – Design Reviews. The design review information specific to the E-Patch is described in the “device-info-amend-3-14-2011.pdf” document found in Amendment 7 (3/17/11), Section 1.6. The SOP explains that (b) (4)

[REDACTED]

The “device-info-amend-3-14-2011.pdf”, section 1.4, describes design verifications below:

[REDACTED] (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

As stated in NuPathe's response to this request for information (Section 1.11.4.1.8 Multiple Module Information Amendment of the NDA), this information will be provided in an update by the end of March 2011. This information was provided in the June 10, 2011, amendment and addresses the deficiency through completing the requested testing.

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.30(f).

Design Validation, 820.30(g)

The firm provided the following documentation to satisfy 820.30(g), Design Validation.

1. SOP QS-003: Design Control and Pharmaceutical Development, Section 3.10 and Section 4.10 titled Design Validation
2. SOP QS-009: Risk Management Procedure

3. Section 3.2.R.4 of the NDA.
4. Section 3.2.R.4.8 of the NDA – relating to Software validation.
5. Sections 5.3.1.1, 5.3.1.2, and 5.3.5.1 – Clinical Trial Reports.

SOP QS-003 section 3.10 defines design validation as (b) (4)
Documentation for the design validation is kept in Section 7 of the design file.

SOP QS-003 section 4.10 states that validations may be performed via (b) (4)

DEFICIENCY 6

You provided SOP QS-003: Design Control and Pharmaceutical Development, Revision .03 in order to satisfy the requirements of 21 CFR 820.30(g), Design Validation. In this SOP, you define what Design Validation is, (b) (4)

(b) (4)

Please provide an updated Design Control Procedure that clearly defines how design validation activities are to be documented in your (b) (4).

The firm provided Section 3.2.R.4 to demonstrate completed design validation. In Section 3, Executive Summary, the firm states that initial clinical studies showed potential for the delivery method to be efficacious, and resulted in the firm optimizing the current waveform to improve delivery of the drug. A pivotal study was performed in 530 human subjects in a multi-center, randomized, parallel group, double-blind, placebo controlled trial where efficacy and tolerability of the treatment was compared with the placebo.

DEFICIENCY 7

You provided section 3.2.R.4, Device (NP101 Electrode Patch), in your NDA submission in order to satisfy the requirements of 21 CFR 820.30(g), Design Validation. In Section 3 – Executive Summary, you describe initial clinical tests and a pivotal study. However, it is not clear from this summary how the study results ensure that the device meets user needs and intended uses. Please provide a summary of how your clinical evaluations demonstrated that the device

meets user needs and intended uses.

The E-Patch contains firmware that controls the administration of the drug – it executes a sleep mode, start test, test mode, active mode, controls system timing, current delivery, self test fail mode, and (b) (4) mode. The firm states that this causes the software to be a major concern, and conducted testing to match that level.

Early clinical studies used a pre-production version of the microcontroller. The controller was replaced by one from a different supplier for further clinical testing. After this, final development included incorporating additional safety protections and reorganizing the firmware code to allow for verification and validation by (b) (4). After Verification and Validation, the code was updated, and reverified and revalidated. The final release changed (b) (4) which had not been factory calibrated. (b) (4) determined that a subsequent Validation and Verification were not necessary due to this (b) (4) change. The rationale for not conducting the verification and validation for this change is documented in Attachment 48: Memo: Verification Impacts of Version (b) (4) of the Patch Software.

DEFICIENCY 8

You provided Section 3.2.R.4: Software in your NDA submission, in order to satisfy software validation requirements of 21 CFR 820.30(g). In section 8.8. Software Development Environment Description, you describe that version (b) (4) of your microcontroller and firmware were used for initial clinical studies demonstrating feasibility, version (b) (4) were used for further clinical testing, while the production version of the firmware is version (b) (4). However, clinical testing demonstrating validation of version (b) (4) to user needs and intended uses, or information demonstrating functional equivalency of the final firmware version (b) (4) to clinically tested versions (b) (4) could not be located in your submission. Please provide documentation that demonstrates that the E-Patch device with the final firmware version has been validated to user needs and intended uses.

Overall Device: The firm provide SOP QS-009: Risk Management Procedure, and form F-QS-041: Risk Report, and the completed form for the E-Patch REP-DHF-NP101-282, in order to satisfy the risk management requirements of 21 CFR 820.30(g).

SOP-QS-009 provides responsibilities related to risk management. (b) (4)

(b) (4)

(b) (4)

. This procedure appears adequate.

Software: The firm included Attachment 17: Software Safety Report and Review Report in the original NDA. The testing was conducted by an external testing firm, (b) (4). The firm determined that their software functions constituted a major concern, and software verification and validation was conducted with this in mind. A risk analysis was provided that described how the firm determined the risk involved for the software.

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.30(g).

Design Transfer, 820.30(h)

The firm provided SOP QS-003: Design Control and Pharmaceutical Development, sections 3.9 and 4.9 in order to satisfy the requirements of 21 CFR 820.30(h), Design Transfer. Section 3.9 defines the Design Transfer as the process of (b) (4)

Design transfer information is located in Section 6 of the design file.

Section 4.9 states that design transfer require consideration of:

(b) (4)

DEFICIENCY 9

You provided SOP QS-003: Design Control and Pharmaceutical Development, sections 3.9 and 4.9 in order to satisfy the requirements of 21 CFR 820.30(h), Design Transfer. In this procedure, you state that design transfer requires

(b) (4)

DEFICIENCY 10

You provided SOP QS-003: Design Control and Pharmaceutical Development, sections 3.9 and 4.9 in order to satisfy the requirements of 21 CFR 820.30(h), Design Transfer. In this procedure, you state that design transfer activities must

consider the Device Master Record. However, it is not clear what documentation is to be included in the Device Master Record. Please provide an updated Design Control procedure that describes what documents comprise the Device Master Record.

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.30(h).

Design Changes, 820.30(i)

The firm provided SOP QS-003: Design Control and Pharmaceutical Development, sections 4.11 to satisfy the requirements of 21 CFR 820.30(i), Design Changes.

Section 4.11, Design Changes, states that as (b) (4)
[Redacted]

[Redacted] (b) (4)

[Redacted] (b) (4)

DEFICIENCY 11

You have provided SOP QS-003: Design Control and Pharmaceutical Development, section 4.11 to satisfy the requirements of 21 CFR 820.30(i), Design Changes. In this procedure, you state that if (b) (4)
[Redacted]

DEFICIENCY 12

You have provided SOP QS-003: Design Control and Pharmaceutical Development, section 4.11 to satisfy the requirements of 21 CFR 820.30(i),

Design Changes. In this procedure, you state that if (b) (4)

DEFICIENCY 13

You have provided SOP QS-003: Design Control and Pharmaceutical Development, section 4.11 to satisfy the requirements of 21 CFR 820.30(i), Design Changes. The procedure should describe when verification is used for certain design changes instead of (b) (4)

However, this information could not be located in your submission. Please provide a procedure that describes how design changes will be determined to require (b) (4), *how this is to be documented, and who is responsible for reviewing and improving design changes.*

The procedure states that SOP QS-002: (b) (4)
This document will be reviewed in the Manufacturing Section of this memo.

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.30(i).

Design History File, 820.30(j)

The firm describes the contents of the Design History File in SOP QS-003: Design Control and Pharmaceutical Development, Section 4.12. It outlines all of (b) (4)

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.30(j).

SECTION II: MANUFACTURING INFORMATION:

Quality System Procedures, 820.20(e)

The firm provided copies of all their quality control procedures relevant to the quality system and manufacturing. They provide a list of all of their quality system procedures.

This includes procedures for:



There is no traditional "Quality Manual" included that summarizes all the quality policies and procedures taking place at the firm. However, the list (outline) of procedures was provided, and all of the necessary parts of the quality system seem to be included in that list.

Some basic issues with quality documentation were noted in this review. No procedures contained a scope to establish a limit of when and where procedures are to be applied.

DEFICIENCY 14

You provided documents including SOP QS-003, TM-0002, TM-0003, TM-0004, SOP QS-009, SOP QS-001, SOP QS-002, SOP QS-004, SOP 10-005, SOP QS-007, SOP QS-008, SOP QS-009, SOP QS-101, SOP QS-011, SOP QS-013, SOPQS-013, SOP 10-015, SOP QS0916, SOP 25-001, SOP QA-002, SOP QA-014, SOP QA-020 and SOP RA-001 in order to satisfy the requirements of 21 CFR 820. In these procedures, you describe the objective, responsibilities, procedure steps, and references related to each procedure. However, none of your procedures contain a scope, which should identify the limits as to when and where a procedure is to be applied. Please provide updated procedures that contain relevant scopes as to when and where the procedures are to be applied.

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.20(e).

Production Flow

A production flow is provided in "device-info-amend-3-14-2011.pdf" that describes (b) (4) production areas involved in production of the E-Patch.

These areas are:



Use of Standards

The firm provided two standards for sampling procedures: ANSI/ASQ Z1.4 and ASQ Z1.9. Other standards were provided in the initial NDA submission, Section 3.2.R.4.2

The standards in Section 3.2.R.4.2 include

Table 1: Standards Used in the Development and Evaluation Process

Recognition List Number	Recognition Number	Standard	Title
013	5-10	(b) (4)	(b) (4)
020	12-8		
020	5-28		
020	9-16		

Purchasing Controls, 820.50

The firm provided SOP QS-012: Purchasing (revision .02) and SOP QS-016:

(b) (4)

SOP QS-012: (b) (4)

(b) (4)

[Redacted] (b) (4)

NOTE - [Redacted] (b) (4)

T [Redacted] (b) (4)

NOTE - [Redacted] (b) (4)

[Redacted] (b) (4)

DEFICIENCY 15

You provided SOP QS-012: Purchasing (revision .02) in order to satisfy the requirements of 21 CFR 820.50, Purchasing Controls. In this SOP, you state that

[Redacted] (b) (4)

Reference is made to "Purchasing Policy 2010_2.0" in this procedure.

DEFICIENCY 16

You provided SOP QS-012: Purchasing (revision .02) in order to satisfy the

requirements of 21 CFR 820.50, Purchasing Controls. In this SOP, you reference "Purchasing Policy 2010_2.0". However, this policy could not be found in your submission. Please provide this Policy, or the location where it may be found in your submission.

NOTE – In the provided procedures, there is no discussion about (b) (4)

SOP QS-016: External Auditing is a procedure that discusses how supplier audits are to occur. It details the responsibilities of QA for (b) (4)

(b) (4)

DEFICIENCY 17

You provided SOP QS-012: Purchasing (revision .02) and SOP QS-016: External Auditing in order to satisfy the requirements of 21 CFR 820.50, Purchasing Controls. In these procedures, you describe how purchases are made by (b) (4)

(b) (4)

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.50.

Production and Process Controls, 820.70

The firm provides MS-009: NP101 Electrode Patch (500001) and controlled drawing 500001: Electrode Patch Assembly. The firm states that the assembly process is controlled by (b) (4)

The firm does not provide environmental or contamination control information for production of the E-Patch. However, given the processes described in assembly of the E-Patch and (b) (4) packaging, it seems that these are processes which should have environmental controls. Of greatest concern are dust levels, required (b) (4) adhesives, etc.

DEFICIENCY 18

You provided the document, "device-info-amend-3-14-2011.pdf", section 2.7: *Production and Process Controls, 820.70*, as a summary discussing your production and process controls as required by 21 CFR 820.70. In this summary, you describe how assembly of the E-Patch is controlled. However, no environmental or contamination controls for manufacture of the E-Patch could be found. Please provide environmental and/or contamination control documentation for assembly of the E-Patch and (b) (4) packaging as required by 21 CFR 820.70(c), *Environmental Control*, and 21 CFR 820.70(e), *Contamination Control*.

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.70.

Inspection, Measuring, and Test Equipment, 820.72

No general procedure for maintaining calibration files and having primary responsibilities for making sure that calibrations are accomplished at specific intervals is provided.

The firm provided four procedures describing how inspection, measuring and test equipment is routinely calibrated, inspected, checked, and maintained.

- a) SOP 75-002: Operation, Maintenance and Calibration of the Electrode Capacity Tester
- b) SOP 75-003: Operation, Maintenance and Calibration of the Electrode Card/Patch Tester
- c) SOP 75-007: Operation, Maintenance and Calibration of the Electrode Patch Connectivity Tester
- d) SOP 75-009: Operation and Maintenance of the (b) (4) Battery Tester

a) SOP 75-002 – This procedure discusses (b) (4)

[REDACTED]

b) SOP 75-003 – This procedure discusses (b) (4)

[REDACTED]

c) SOP 75-007 – This procedure discusses (b) (4)

d) SOP 75-009 – This procedure describes operation and maintenance of the (b) (4) Battery Tester, which tests the (b) (4). No information regarding calibration could be found.

DEFICIENCY 19

You provided SOP 75-009: Operation and Maintenance of the (b) (4) Battery Tester to satisfy the requirements of 21 CFR 820.72, Inspection, Measuring, and Test Equipment. In this procedure, you describe how to operate the Battery Tester. However, the procedure does not describe the need to calibrate the instrument, and if it is required, how often, by whom, and where the calibration record will be stored. Please provide a procedure for the (b) (4) Battery Tester that addresses the requirements for calibration of 21 CFR 820.72(b), Calibration.

DEFICIENCY 20

You provided four procedures, SOP 75-002, SOP 75-003, SOP 75-007, and SOP 75-009. In these procedures, you describe maintenance, operation, and calibration of four different pieces of test equipment. However, it is not clear if these procedures describe all of your inspection, measuring, and test equipment, or if they represent a sample. Please provide a list of other inspection, measuring, and test equipment used for the manufacture of the E-Patch and (b) (4) Packaging, and a procedure that describes how your calibration records are kept for your equipment.

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.72.

Process Validation, 820.75

The firm provides a list of processes to validate in the “device-info-amend-3-14-2011.pdf” document, section 2.7 Process Validation, 820.75. Those processes are – (b) (4)

The Electrode Patch Assembly and (b) (4) packaging processes are reviewed, as those are the finished devices.

Section 2.7.4 discusses the Electrode Patch (E-Patch) assembly process. The critical parameters of the E-Patch assembly process are: (b) (4)

[Redacted] (b) (4)

Section 2.7.5 discusses the [Redacted] (b) (4) Packaging process. Critical parameters are identified to be – [Redacted] (b) (4)

[Redacted]

[Redacted] (b) (4)

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.75.

Process Validation, 820.75(a)

The firm provides plans for the validation of the following

A. Electrode

[Redacted] (b) (4)

DEFICIENCY 21

You provide a process validation plan in “device-info-amend-3-14-2011.pdf,” section 2.8 Process Validation, 820.75(a). In this plan, you describe your Electrode testing validations to be conducted from [Redacted] (b) (4)

[Redacted]

Please provide a process validation procedure for your Electrode testing validations that include statistical rationale for your [Redacted] (b) (4) plan.

Acceptance criteria are provided for the electrode as – [Redacted] (b) (4)

DEFICIENCY 22

You provide a process validation plan in "device-info-amend-3-14-2011.pdf," section 2.8 Process Validation, 820.75(a). In this plan, you describe your acceptance criteria to be (b) (4). However, these criteria appear to be subjective, rather than objective and measurable. Please provide an updated Electrode process validation plan and process validation procedure that provides objective and measurable acceptance criteria.

B. E-Patch

(b) (4)

DEFICIENCY 23

You provide a process validation plan in "device-info-amend-3-14-2011.pdf," section 2.8 Process Validation, 820.75(a). In this plan, you describe how the E-Patch process will be validated. However, you have not provided a procedure for this validation. Please provide a validation procedure for your E-Patch process. As a reminder, process validations must be completed prior to the pre-approval inspection.

C. (b) (4) Packaging

(b) (4)

DEFICIENCY 24

You provide a process validation plan in "device-info-amend-3-14-2011.pdf," section 2.8 Process Validation, 820.75(a). In this plan, you describe how the (b) (4) Packaging will be validated with (b) (4). However, no statistical rationale could be found in your plan for why (b) (4).

(b) (4). Please provide an updated process validation plan and a process validation procedure for (b) (4) Packaging that contains a statistical rationale for your (b) (4) plan.

DEFICIENCY 25

You provide a process validation plan in "device-info-amend-3-14-2011.pdf," section 2.8 Process Validation, 820.75(a). In this plan, you describe that your packaging will be validated. However, no acceptance criteria could be found for this validation. Please provide an updated process validation plan and a process validation procedure for (b) (4) Packaging that contains objective and measureable acceptance criteria.

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.75(a).

Receiving Acceptance Activities, 820.80(b)

The firm has significant deficiencies within their supplier controls in that no information was provided for how suppliers are evaluated or approved for providing services. However, the firm does supply (b) (4).

(b) (4)
in accordance with SOP QA-014: Release of Batch Record Processed Material.

Materials received at NuPathe are governed by SOP 10-005 – Materials Control. Specific acceptance criteria for individual (b) (4)

(b) (4)

DEFICIENCY 26

You provided "device-info-amend-3-14-2011.pdf," Section 5.1 Receiving Acceptance Activities to describe receiving acceptance activities at (b) (4) at NuPathe's facilities. In your description, you state that (b) (4)

(b) (4) However, you have not provided sufficient documentation of (b) (4) are being performed. Please provide either documentation of (b) (4)

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.80(b).

Final Acceptance Activities, 820.80(d)

DEFICIENCY 27

You provided "device-info-amend-3-14-2011.pdf," Section 5.2 Final Acceptance Activities, 820.80(d) to describe (b) (4) at NuPathe's facilities. In your description, you state that (b) (4) However, you have not provided sufficient documentation of (b) (4)

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.80(d).

Nonconforming Products, 820.90

The firm provided the following procedures that relate to nonconforming product.

1. SOP QS-011: Non-Conformance and CAPA Management
2. SOP QA-002: Processing Marketed Product Related Complaints and Inquiries
3. SOP QA-014: Release of Batch Record Processed Material

SOP QS-011 - (b) (4)

Section 3.2: Product or Material Non-Conformance describes definitions for the various types of nonconformances.

Section 4.0: Identification and Notification of Non-Conformances and Deviations - (b) (4)

[REDACTED] (b) (4)

Section 5.0-5.3 describes how [REDACTED] (b) (4)

SOP QA-002 – This procedure governs [REDACTED] (b) (4)

SOP QA-014 – This procedure describes the purpose of [REDACTED] (b) (4)

The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.90.

Corrective and Preventive Action (CAPA), 820.100

The firm has provided SOP QS-011: Non-Conformance and CAPA Management to satisfy the requirements of 21 CFR 820.100. This procedure was reviewed here in the previous section (Nonconforming Product).

SOP QS-011 addresses [REDACTED] (b) (4)

DEFICIENCY 28

You provided SOP-QS-011: Non-Conformance and CAPA Management to satisfy the requirements of 21 CFR 820.100. In this procedure, you describe how [REDACTED] (b) (4)

11 [REDACTED] Please provide an updated CAPA procedure that

describes how a determination to conduct a corrective or preventive action is conducted.

DEFICIENCY 29

You provided SOP-QS-011: Non-Conformance and CAPA Management to satisfy the requirements of 21 CFR 820.100. In this procedure, you describe



Please provide a CAPA procedure that addresses all the requirements of 21 CFR 820.100, Corrective and Preventive Action (CAPA).

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.100.

Complaint Files, 820.198

The firm is reporting under adverse drug reporting requirements of 21 CFR 314.80, which is the appropriate adverse reporting procedure for drugs.

DEFICIENCY 30

You provide SOP QA-002: Processing Marketed Product Related Complaints and Inquiries, to satisfy the requirements of 21 CFR 820.198, Complaint Files. In this procedure, you cite SOP RA-013 as the procedure used by



DEFICIENCY 31

You provide SOP QA-002: Processing Marketed Product Related Complaints and Inquiries, to satisfy the requirements of 21 CFR 820.198, Complaint Files. In this procedure, (b) (4)

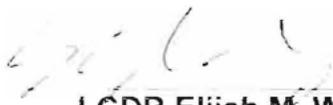
[Redacted]

[Redacted]

Please provide a complaint file procedure that satisfies these requirements of 21 CFR 820.198, Complaint Files.

The procedures provided by the firm have inadequately addressed the requirements of 21 CFR 820.198.

Compliance Reviewer:



LCDR Elijah M. Weisberg, MSE

Prepared: **EMWeisberg** : 5/25/2011
Reviewed: MKrueger: 7/12/2011
Lead Reviewer: **FMLast:date**
Co- Reviewer: **FMLast:date**

Final: **FMLast: date**

cc:

WO66-3659 Weisberg OPMD/DOEB
WO66-1564 Pamidimukkala

OC Doc. No.: CDER Global Summit #202278

Doc#125 024V 3.00; 02/16/2011

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

/s/

TESHARA G BOUIE

07/14/2011

PMQ is checking this review into DARRTS on behalf the CDRH reviewer, Elijah Weisberg.

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: May 6, 2011

TO: Lana Chen, Regulatory Health Project Manager
Nushin Todd, M.D., Ph.D. Medical Officer
Division of Neurology Products

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202-278

APPLICANT: NuPathe Inc.

DRUG: Zeltrix (sumatriptan)

NME: No:

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of Acute Migraine

CONSULTATION REQUEST DATE: February 8, 2011

DIVISION ACTION GOAL DATE: August 29, 2011

PDUFA DATE: August 29, 2011

I. BACKGROUND:

NeuPathe Inc. submitted this application for the use of Sumatriptan Iontophoretic Transdermal Patch (NP101) in the treatment of adult patients with migraine headache. One pivotal study, Study NP101-007, was submitted in support of the application. The sponsor has requested approval of the new formulation to treat migraine headache.

Sumatriptan is a triptan drug including a sulfonamide group which was originally developed by Glaxo for the treatment of migraine headaches. It belongs to a class of drugs called selective serotonin receptor agonists. Migraine headaches are believed to result from dilatation of blood vessels in the brain. Females more frequently suffer from migraine headache than males. Migraine headache is associated with a painful vasodilation of cranial vessels and is typically associated with certain characteristics such as pain of moderate or severe intensity, worsening with physical activity and pulsating pain. In addition to headache pain, migraine is also associated with other symptoms, including nausea, vomiting, phonophobia, and photophobia, and other visual symptoms such as spots of light, zigzag lines, or graying out of vision.

Iontophoresis is a non-invasive drug delivery method that, using low electrical current, moves solubilized drugs across the skin to the underlying tissue without an injection. The rate and amount of delivery can be precisely controlled, so that doses may be automatically delivered in a pre-programmed manner. Adverse events due to iontophoretic delivery may include local erythema, irritation, and pruritus.

The sponsor has provided data from Study NP101-007, in support of the approval of the new iontophoretic technology to deliver sumatriptan. The goal of the NP101 development program was to address unmet needs of the current sumatriptan formulations. NP101 is a thin, disposable, single-use device with self-contained electronic controller and a battery power source designed to deliver sumatriptan transdermally.

Protocol NP101-007

This was a randomized, parallel group, double-blind, placebo controlled study designed to compare the efficacy and tolerability of NP101 to a placebo iontophoretic transdermal patch.

The primary objective of this study was to assess the proportion of subjects who are headache pain free at two hours after patch activation. Key secondary objectives are to assess the proportion of subjects who are nausea free at 2 hours after patch activation.

Adult subjects who met the enrollment criteria were randomized in a 1:1 ratio and stratified by race [white and non-white] via an Interactive Voice Response System (IVRS) into one of two treatment groups:

1. NP101-sumatriptan iontophoretic transdermal patch, or
2. Placebo iontophoretic transdermal patch

Subjects remained in the study until they were treated for one migraine headache with a study patch or for two months after randomization, whichever occurred first. Subjects rated their

baseline headache by recording the pain severity in their diaries on a scale 0 = none to 3=severe.

The review division requested inspection of one clinical investigator for the pivotal study (Protocol NP101-007) as data from the protocol are considered essential to the approval process. One domestic investigator was chosen to cover the protocol. This site was targeted for inspection due to enrollment of a relatively large number of subjects (2nd largest), and because estimate of percentage of headache pain free for treatment group was numerically larger than the average (6/16= 37.5% versus an average of 40/226=17.7%) when compared to other sites.

II. RESULTS (by protocol/site):

Name of CI, site # and location	Protocol and # of subjects	Inspection Dates	Final Classification
David Kudrow, M.D. California Medical Clinic, 2001 Santa Monica Blvd., Suite 880W Santa Monica, CA 90404 Site# 115	Protocol NP101-007 Number of subjects listed 35	2/28- 3/3/11	NAI

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol NP101-007

**1. David Kudrow, M.D.
Santa Monica, CA90404**

a. What Was Inspected: At this site, a total of 36 subjects were screened and 3 subjects were reported as screen failures. Thirty three (33) subjects were randomized and 33 subjects completed the double-blind phase of the study. There were no deaths and no under-reporting of adverse events. Review of Informed consent documents for all records reviewed, verified that subjects signed prior to enrollment.

A review of the medical records/source documents was conducted. The medical records for 18 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory test results, and the use of concomitant medications. Source documents were

compared to case report forms and to data listings, including primary efficacy endpoints and adverse events listings. In addition, IRB records and sponsor correspondence were reviewed.

b. General observations/commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Kudrow. Our investigation found 5 of the 18 subjects' record reviewed revealed that the subjects did not follow their skin assessment score until 0. However, the clinical investigator did assess the condition of the skin (patch site) until there was no more redness and the score was confirmed to be 0. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the pending application.

c. Assessment of Data Integrity: The data, in support of the clinical efficacy and safety at Dr. Kudrow's site are considered reliable and appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

One clinical investigator was inspected in support of this application. The inspection of Dr. Kudrow revealed no adverse finding. Overall, the data collected in support of this application are considered reliable and acceptable.

{See appended electronic signature page}

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/s/

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05/11/2011

TEJASHRI S PUROHIT-SHETH
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