

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-504

**ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE**

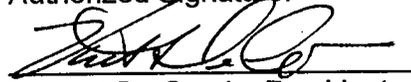
13.0 PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

13.1 Patent US 5,246,418

- 13.1.1 Title: Iontophoresis System Having Features For Reducing Skin Irritation
- 13.1.2 Expiration Date: December 17, 2011
- 13.1.3 Type of Patent: Drug Product
- 13.1.4 Name of Owner: Vyteris, Inc.
- 13.1.5 Declaration:

The undersigned declares that US Patent No. 5,246,418 covers the formulation, composition, and/or method of use of the *Northstar Lidocaine Iontophoretic Drug Delivery System*. This product is the subject of this application for which approval is sought.

- 13.1.6 Authorized Signature:


Vincent De Caprio, President

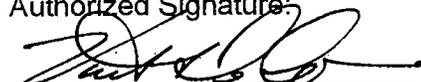
8/28/02
Date

13.2 Patent US 5,873,850

- 13.2.1 Title: Locking And Disfiguring Mechanism For An Iontophoretic System
- 13.2.2 Expiration Date: May 29, 2017
- 13.2.3 Type of Patent: Drug Product
- 13.2.4 Name of Owner: Vyteris, Inc.
- 13.2.5 Declaration:

The undersigned declares that US Patent No. 5,873,850 covers the formulation, composition, and/or method of use of the *Northstar Lidocaine Iontophoretic Drug Delivery System*. This product is the subject of this application for which approval is sought.

- 13.2.6 Authorized Signature:


Vincent De Caprio, President

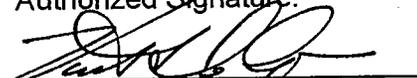
8/28/02
Date

13.3 Patent US 6,377,847

- 13.3.1 Title: Iontophoretic Drug Delivery Device and Reservoir and Method of Making Same
- 13.3.2 Expiration Date: September 30, 2013
- 13.3.3 Type of Patent: Drug Product
- 13.3.4 Name of Owner: Vyteris, Inc.
- 13.3.5 Declaration:

The undersigned declares that US Patent No. 6,377,847 covers the formulation, composition, and/or method of use of the *Northstar Lidocaine Iontophoretic Drug Delivery System*. This product is the subject of this application for which approval is sought.

- 13.3.6 Authorized Signature:



Vincent De Caprio, President

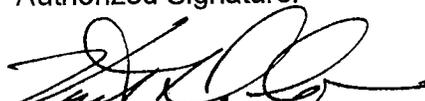
8/28/02
Date

13.4 Patent US 6,385,488

- 13.4.1 Title: Circuits for Increasing the Reliability of an Iontophoretic System
- 13.4.2 Expiration Date: May 20, 2019
- 13.4.3 Type of Patent: Drug Product
- 13.4.4 Name of Owner: Vyteris, Inc.
- 13.4.5 Declaration:

The undersigned declares that US Patent No. 6,385,488 covers the formulation, composition, and/or method of use of the *Northstar Lidocaine Iontophoretic Drug Delivery System*. This product is the subject of this application for which approval is sought.

- 13.4.6 Authorized Signature:



Vincent De Caprio, President

8/28/02
Date

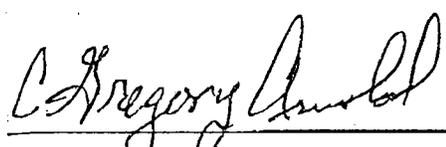
Vyteris, Inc.
Northstar Lidocaine Iontophoretic Drug Delivery System

Final
Patent Certification

14. PATENT CERTIFICATION

No Relevant Patent Statement

In the opinion and to the best knowledge of Vyteris, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application *were* conducted or that claim the use of such drug or drugs by an iontophoretic drug delivery system.



C. Gregory Arnold
Vice President, Manufacturing Operations
Vyteris, Inc.

Date 5/6/04

14. PATENT CERTIFICATION

No Relevant Patent Statement

In the opinion and to the best knowledge of Vyteris, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim the use of such drug or drugs.



Vincent DeCaprio
President, Vyteris, Inc.

9/11/02
Date

Trade Name LidoSite™ Topical System comprised of the LidoSite™ Patch (Lidocaine HCl / Epinephrine topical iontophoretic patch) 10%/0.1% and the LidoSite™ Controller

Generic Name Lidocaine HCl / Epinephrine topical iontophoretic patch 10%/0.1%

Applicant Name Vyteris, Inc. HFD- 170

Approval Date May 4, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA? YES/x/ NO /___/

b) Is it an effectiveness supplement? YES /___/ NO /x/

If yes, what type(SE1, SE2, etc.)?

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

YES /x/ NO /___/

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

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe

the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /__/ NO /X/

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

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

YES /___/ NO /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

_____ YES / / NO /X/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/ N/A

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

2. Combination product.

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

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s). (The following NDAs contain either lidocaine or epinephrine or both):

NDA # 19-941 (Emla Cream)

NDA # 20-962 (Emla Disc)

NDA # 20-530 (Iontocaine)

NDA # 20-612 (Lidoderm)

NDA # 6-488, 8-816, 21-380, 21-381 (Xylocaine and Xylocaine with Epinephrine) products

NDA # 20-575 (DentiPatch Patch)

NDA # 21-383 (Citanest with epinephrine)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

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

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

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

YES /___/ NO /X/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's

conclusion? If not applicable, answer NO.

YES /___/ NO /X/

If yes, explain:

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

YES /___/ NO /X/

If yes, explain:

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

Investigation #1, Study # BDTs-99-67

Investigation #2, Study # BDTs-99-68

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

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

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

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

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

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

Investigation #1 YES /___/ NO / X /
Investigation #2 YES /___/ NO / X /

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

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

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

Investigation #1, Study # BDTs-99-67

Investigation #2, Study # BDTs-99-68

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

substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- (a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor? Note: Sponsor states in NDA cover letter that these studies were carried out by or for them for this NDA.

Investigation #1

IND # 48, 365 YES / NO /

Investigation #2

IND # 48, 365 YES / NO /

NOTE: The original sponsor listed for the IND is Becton Dickinson Transdermal Systems. Vyteris was spun-off as a new company in November 2001.

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

Investigation #1

YES / Explain ! NO /

Investigation #2

YES / Explain ! NO / Explain

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

conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

Kimberly Compton, Project Mgr., and Parinda Jani, CPMS
Signature of Preparers

5-6-04
Date

Bob Rappaport, M.D.,
Signature of Division Director

Date

cc:
Archival NDA
HFD-170/DFS
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Bob Rappaport
5/6/04 04:19:34 PM

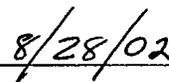
16 DEBARMENT CERTIFICATION

In compliance with the Generic Drug Enforcement Act of 1992, Section 306(k)(1) of the act (21 U.S.C. 335a(k)(1)), we, Vyteris Inc., state the following with respect of this new drug application:

Vyteris Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with this application for Northstar Lidocaine Iontophoretic Drug Delivery System for non-invasive dermal anesthesia.



Vincent De Caprio, President



Date

Vyteris, Inc.

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-504

Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: May 9, 2002 Action Date: May 5, 2004

HFD-170 Trade and generic names/dosage form: LidoSite™ Topical System comprised of the LidoSite™ Patch (Lidocaine HCl / Epinephrine topical iontophoretic patch) 10%/0.1% and the LidoSite™ Controller

Applicant: Vyteris, Inc. Therapeutic Class: Topical Anesthetic

Indication(s) previously approved: N/A

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

Number of indications for this application(s): indicated for use on normal intact skin to provide local analgesia for superficial dermatological procedures such as venipuncture, intravenous cannulation, and laser ablation of superficial skin lesions, on patients 5 years of age and older.

Indication #1:

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

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see

Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

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

- Formulation needed
- Other:

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

Section C: Deferred Studies

Age/weight range being deferred:

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

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed-sponsor has agreed to conduct studies in this population as a Post-Marketing commitment.
- Other:

Date studies are due (mm/dd/yy): April 30, 2007

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 6 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Comments:

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

This page was completed by:

Kimberly Compton/5-4-04
Regulatory Project Manager

cc: NDA 21-504
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze

(revised 9-24-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337**

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

/s/

Parinda Jani
5/6/04 02:58:34 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-504	Efficacy Supplement Type SE-	Supplement Number
Drug: LidoSite™ Topical System comprised of the LidoSite™ Patch (Lidocaine HCl / Epinephrine topical iontophoretic patch) 10%/0.1% and the LidoSite™ Controller		Applicant: Vyteris, Inc.
RPM: Kim Compton		HFD-170 Phone # 301-827-7410
Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): Xylocaine (N 6-488)
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		May 10, 2004 (AP)
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		N/A

❖ Exclusivity (approvals only)		
• Exclusivity summary		X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!		() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		Filing Rvw-4/17/03
General Information		
❖ Actions		
• Proposed action		(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)		AE on July 25, 2003
• Status of advertising (approvals only)		(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications		
• Press Office notified of action (approval only)		() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated		(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))		
• Division's proposed labeling (only if generated after latest applicant submission of labeling)		X (as found in the AP letter)
• Most recent applicant-proposed labeling		
• Original applicant-proposed labeling		X, cycle 1 and cycle 2
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)		X (See ODS review in "Labels" section)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)		
❖ Labels (immediate container & carton labels)		
• Division proposed (only if generated after latest applicant submission)		
• Applicant proposed		X
• Reviews		X (ODS), cycle 1 and 2
❖ Post-marketing commitments		
• Agency request for post-marketing commitments		
• Documentation of discussions and/or agreements relating to post-marketing commitments		X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)		X
❖ Memoranda and Telecons		X
❖ Minutes of Meetings		
• EOP2 meeting (indicate date)		#1= 9/16/99 #2=2/27/00
• Pre-NDA meeting (indicate date)		X- 4/24/01
• Pre-Approval Safety Conference (indicate date; approvals only)		N/A
• Other		1/13/99 ("Guidance meeting")

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	X (7/25/03-cycle 1), (5-5-04-cycle 2)
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	X (7/25/03-cycle 1), (4/26/04-cycle 2)
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Included in Clinical Review (see above)
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) (indicate date for each review)	X (June 23, 2003-cycle 1 only)
❖ Biopharmaceutical review(s) (indicate date for each review)	X (6/30/03-cycle 1), (2/27/04-cycle 2)
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) (indicate date for each review)	X (7/25/03-cycle 1), (5/3/04-cycle 2)
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	See 7/25/03 CMC Review, Pg. 110
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	X (7/3/03-cycle 1 only)
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable () Withhold recommendation
❖ DMF Reviews (4)	X (7/25/03-cycle 1), (4-30-04-cycle 2)
❖ Methods validation	() Completed (X) Requested () Not yet requested
❖ CDRH review	X (6/11/03-cycle 1), (3-10-04-cycle 2)
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	X (7/24/03)

❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	
❖ CAC/ECAC report	

Compton, Kimberly

From: George Baskinger [gbaskinger@vyteris.com]
Sent: Monday, May 03, 2004 6:54 PM
To: Comptonk@cder.fda.gov
Subject: NDA 21-504 Agreement 3 May 2004

CMC
"agreements"

Kimberly,

The Agency has requested Vyteris to agree to Items 1 and 2 below:

1. The acceptance criteria for the physical quality attributes of the patch, namely the cathode and anode probe tack, the apparent compressive modulus of the electrodes, and the probe tack of the adhesive are based on

these are considered

tentative in nature. Similarly, the acceptance criteria for the anode-specific and the cathode-specific conductivities with their additional allowances are considered tentative in nature. Provide an agreement that following accrual of the data from commercial batches of the drug product, these specifications will be revised and tightened to reflect the observed data as appropriate.

**APPEARS THIS WAY
ON ORIGINAL**

2. Since the test method for the in vitro drug release is currently being developed, provide an agreement that within one year from

the date of the action letter, a test method will be developed, validated and established as part of the drug product specifications and submitted as a Prior Approval Supplement.

Based on the discussion with yourself and Dr. Duffy during our teleconference this afternoon, Vyteris agrees to the following:

1. Vyteris agrees to accrue data for commercial batches of drug product for the cathode and anode probe tack, the apparent compressive modulus

of the
reservoirs (electrodes), the probe tack of the adhesive,
and
the anode-specific
and cathode-specific conductivities with data based on eight
lots of
subcomponents. These drug product specifications will be
revised and
tightened to reflect the observed data as appropriate.

2. Vyteris agrees to develop, validate, and establish as
part
of the drug product
specifications an in-vitro drug release test method within
eighteen months from
the date of the action letter. Vyteris will make every
effort
to submit the method
prior to the commitment date. The method will be submitted
as a
Prior Approval
Supplement.

Regards,

George M. Baskinger
Manager, Quality Management/
Regulatory Compliance
Vyteris, Inc.
13-01 Pollitt Drive
Fair Lawn, NJ 07410

Phone: (201) 703-2420
Fax: (201) 703-2295
email: gbaskinger@Vyteris.com

Office of Drug Safety

MEMO

Cycle 2

To: Bob Rappaport, M.D.
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products; HFD-170

From: Scott Dallas, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support; HFD-420

Through: Denise Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support; HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support; HFD-420

CC: Kim Compton
Project Manager, Division of Anesthetic, Critical Care, and Addiction Drug Products; HFD-170

Date: February 25, 2004

Re: ODS Consult 03-0167-2;
(Lidocaine Hydrochloride and Epinephrine Transdermal System)
10%/0.1%;
NDA 21-504

This memorandum is in response to a January 28, 2004 request from your Division for a re-review of the proposed labels and labeling. DMETS also re-evaluated the proposed name, LidoSite, since our previous review of the proposed proprietary name is not within 90 days of the tentative approval of this NDA. (PDUFA date: May 10, 2004)

The Division of Medication Errors and Technical Support (DMETS) has not identified any additional proprietary or established names that have the potential for confusion with LidoSite since we conducted our initial review dated July 24, 2003, that would render the name objectionable. In addition, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the proposed name, LidoSite, acceptable from a promotional perspective.

In the re-review of the proposed labels and labeling for LidoSite, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user errors.

1. General Comments

The established name is currently presented as _____ on the labels and labeling. DMETS has recommended that the Division of Anesthetic, Critical Care, and Addition Drug Products consult with the CDER Labeling and Nomenclature Committee for the proper nomenclature of the established name.

2. Patch Label (RDW – 0017 Rev A 09/29/03)

3. Pouch Primary Package Labeling (RDW – 0003 and 0004 Rev B 09/29/03)

4. Carton Labeling (25 pouched patch units: RDW – 0006 and 0007 Rev B 09/29/03)

5. Controller Label (RDW – 0011 Rev B 09/29/03)

7. Package Insert Labeling (Rev. July 2003)

In summary, DMETS has no objections to the use of the proprietary name and considers this a final name review. DDMAC finds the name acceptable from a promotional perspective. DMETS recommends the Division of Anesthetic, Critical Care, and Addition Drug Products (HFD-170) consult with the CDER Labeling and Nomenclature Committee (LNC) for the proper nomenclature of the established name. DMETS recommends implementation of the label and labeling revisions outlined above.

However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the project manager, Sammie Beam at 301-827-3242.

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

/s/

Scott Dallas
3/10/04 07:44:40 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/10/04 11:44:34 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/10/04 02:10:27 PM
DRUG SAFETY OFFICE REVIEWER

DATE: March 10, 2004
FROM: K. Lee, M. D., Medical officer
FDA / CDRH / ODE / DGRND / REDB
SUBJECT: Vyteris NDA 21504
TO: The file

Mark A. Miller
3/10/04

Final Comments by K. Lee

The sponsor responded to manufacturing deficiency of electrodes and described the manufacturing process, electrode specification and stability tests of electrical parameters, such as leakage currents, pH of electrodes and tack specifications. The sponsor had done stability test with samples (n=5, page 408) from three batches using regression analyses and concluded that the samples met the lower or upper 95 confidence intervals of the sponsor's specification up to 24 months at different conditions. The number of samples was 5 for each test for each regression analysis. The sponsor's responses to manufacturing deficiency of electrodes and stability tests are adequate.

I have neither concerns nor issues on the specifications, manufacturing of electrodes, or on stability tests of device aspects, based on the review and the sponsor's statistical analyses. It seems that the sponsor's conclusions on the stability analyses were reasonable and that their specification of the device (electrical or other device related parameters) seems acceptable.

K. Lee, M.D.
Medical Officer

Kyung Nam Lee

The following are the summary of the FDA deficiency and the sponsor's response regarding the device aspects of this NDA.

FDA deficiency item 9:

Provide the detailed manufacturing procedure of the electrode subassembly since it is a critical component of the patch. Alternatively, provide a reference to a drug master file (or device master file) from its vendor.

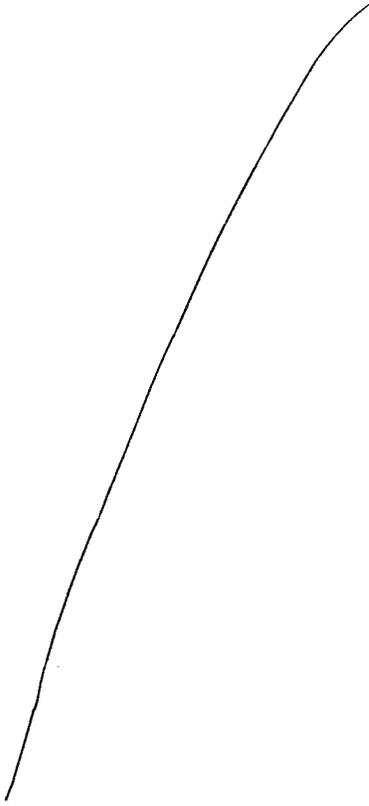
The sponsor's Response to item 9:

15 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



Conclusion:

Thus, although the protocol was not followed at the time points (i.e. the evaluation was not done at all the intermediate time points) required for the appearance evaluation, the data indicates that the appearance specification is met well beyond the proposed shelf life of 24 months.

5.6 Statistical Data Summary

A summary of the regression analyses is presented in the following pages as Table VIb.

Comments by K. Lee

The sponsor responded to manufacturing deficiency of electrodes and described the manufacturing process, electrode specification and stability tests of electrical parameters, such as leakage currents, pH of electrodes and tack specifications. The sponsor had done stability test with samples (n=5, page 408) from three batches using regression analyses and concluded that the samples met the lower or upper 95 confidence intervals of the sponsor's specification up to 24 months at different conditions. The number of samples was 5 for each test for each regression analysis. The sponsor's responses to manufacturing deficiency of electrodes and stability tests are adequate. I have neither concerns nor issues on the specifications, manufacturing of electrodes, or on stability tests of device aspects, based on the review and the sponsor's statistical analyses. It seems that the sponsor's conclusions on the stability analyses were reasonable and that their specification of the device (electrical or other device related parameters) seems acceptable.


K. Lee, M.D.
Medical Officer

cycle 2

For Consulting Center Use Only:

Date Received: 1/30/04
Assigned to: KKL
Date Assigned: 1/30/04
Assigned by: JRS
Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH
Division: DGRND
Mail Code: HFD-170
Consulting Contact Name: Pauline Fogarty, ADPO
Building/Room #: Comp. Rm 350E
Phone #: 301-594-1184
Fax #: 301-594-2358
Email Address: PXF@cdrh.fda.gov
RPM/CSO Name and Mail Code: N/A

From (Originating Center):

Center: CDER
Division: DACCADP
Mail Code: HFD-170
Requesting Reviewer Name: Ravi Harpanhalli, Ph.D.
Requesting Reviewer's Concurring Supervisor's Name: Dale Koble, Ph.D.
Building/Room #: PKLN 9B-45
Phone #: 301-827-7440
Fax #: 301-443-7068
Email Address: harapanhalli@cder.fda.gov
RPM/CSO Name: Kim Compton (comptonk@cder.fda.gov)
(consult initialed by PJ, CPMS, 4-18-03)

** Please advise consulting Division of assigned reviewer as soon as they are identified so they may be included in the review process.

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 1-28-04

Requested Completion Date: March 1, 2004

Submission/Application Number: N 21-504
(Not Barcode Number)

Submission Type: NDA-combination product
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Submission Receipt Date: 11-5-03

Official Submission Due Date: 5-10-04

Name of Product: Northstar Lidocaine Iontophoretic Drug Delivery System Name of Firm: Vyteris, Inc.

Intended Use: Administration of lidocaine HCl to provide local dermal anesthesia on normal intact skin. Indicated for use in patients 5 years of age and older

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

The documents associated with this application are available in CDER's Electronic Document Room (EDR), accessible through the CDER Intranet. Please contact the Project Manager if you require assistance accessing these documents.

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

This iontophoretic drug delivery system has two components, the patch (including electrodes and reservoirs) and the controller. The controller was submitted as a 510(k) to CDRH and the patch is described in the NDA. It appears that there will be some overlap between the NDA and the 510(k) with regard to the electrical aspects of the patch.

The patch consists of electrode subassembly and the anode and cathode reservoirs and these are described in the NDA. The specifications for the patch release include physical, chemical, microbiological, and electrical testing. The latter consist of the specific capacity of the patch, dielectric leakage current, patch leakage current, and patch conductance including trace conductance and hydrogel/electrode conductivity.

We request that CDRH review the section on the manufacture of electrode subassembly (design controls etc.) and the electrical testing of the patch and the specifications as they seem to be directly related to the functioning of the controller, which is being reviewed by CDRH under a 510(k). This submission is a response to an "Approvable" letter and is partially in paper and partially an electronic submission accessed from the electronic document room (EDR). Relevant sections from the original NDA were described under section 4.2.9.2 (Manufacture), 4.2.10 (Drug Product specifications) and the batch records. A paper copy of the response is being sent with a hard copy of this consult

The electrode subassembly is manufactured by the following manufacturer:

—————>

If you have any questions please contact the CMC reviewer, Dr. Ravi Harapanhalli at 301-827-7440.

The Division seeks CDRH's response to the posed request as well as any other related comments on the topic. The Division will provide appropriate feedback to the sponsor based on CDRH's response.

Type of Request: Consultative Review Collaborative Review

**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/

Kimberly Compton
1/28/04 07:18:41 PM

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED: May 14, 2003

DUE DATE: July 18, 2003

ODS CONSULT #: 03-0167

TO: Bob Rappaport, MD
Acting Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

THROUGH: Kim Compton
Regulatory Project Manager
HFD-170

PRODUCT NAME:

LidoSite

10%/0.1%

NDA # 21-504

NDA SPONSOR:

Vyteris Inc.

SAFETY EVALUATOR: Scott Dallas, R.Ph.

SUMMARY: In response to a consult from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name, "LidoSite", to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATION:

1. DMETS has no objection to the use of the proprietary name, "LidoSite".
2. DMETS recommends implementation of the label revisions outlined in Section III of this review.
3. DMETS recommends the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) consult with the CDER Labeling and Nomenclature Committee (LNC) for the proper nomenclature of the established name.
4. DDMAC found the name "LidoSite" acceptable from a promotional perspective.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax (301) 443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Building Room 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 24, 2003

NDA NUMBER: 21-504

NAME OF DRUG: LidoSite

10%/0.1%

NDA SPONSOR: Vyteris Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) for an assessment of the proposed proprietary name, LidoSite. The draft patch label, carton labeling and package insert labeling were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

LidoSite is the proposed tradename for a transdermal patch containing lidocaine hydrochloride 10% and epinephrine 0.1%. The contents of the patch are to be administered through a process known as iontophoresis to

A controller is required to administer the medication and under normal circumstances the medication is administered over a 10 minute interval. The duration of anesthesia may last for 30 minutes. This product is only intended to administered by healthcare professionals in a healthcare setting and is not intended to be dispensed to patients for self-administration.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound alike or look alike to "LidoSite" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted⁴. The Saegis⁵ Pharma-In-Use database was

¹ MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, MO.

³ The Drug Product Reference File [DPR], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/main/trademarks.htm>

⁵ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted prescription analysis studies, involving healthcare practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

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

1. DDMAC did not have any concerns with the promotional aspects of the name, "LidoSite".
2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with "LidoSite". These products are listed in Table 1, along with the dosage forms available and usual dosage.

TABLE 1

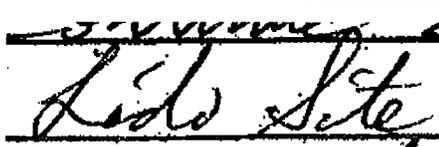
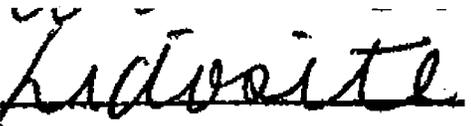
Product Name	Generic name, Dosage form(s), and Strength(s)	Indication and Usual adult dose*	Other**
LidoSite	Lidocaine Hydrochloride/Epinephrine, Transdermal Patch, 10%/0.1%	Indicated to — — Usual adult dose: Administer the contents of one patch by a controller over a 10 minute interval.	
Lithostat	Acetohydroxamic Acid Tablet, 250 mg	Indicated as adjunctive therapy to treat chronic urea-splitting urinary infection. Usual adult dose: Take 1 tablet by mouth 3 to 4 times a day. A total daily dose of 10 to 15 mg/kg/day.	S/A per DMETS
Lodosyn	Carbidopa, Tablet, 25 mg	Indicated for the treatment of the symptoms of idiopathic Parkinson's disease, postencephalitic parkinsonism and symptomatic parkinsonism. Dose: Individually adjusted for individuals requiring titration of cardidopa and levodopa. It may be dosed one time or multiple times a day, but not to exceed 200 mg per day.	S/A per DMETS

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

B. PRESCRIPTION ANALYSIS STUDIES

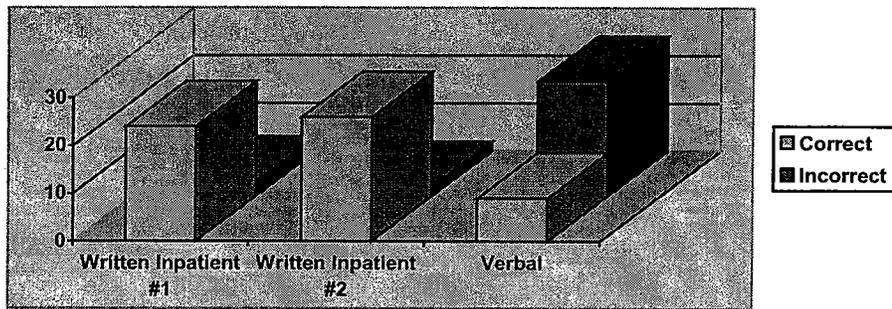
1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of LidoSite with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 127 health care professionals (nurses, pharmacists, and physicians) for LidoSite. This exercise was conducted in an attempt to simulate the prescription ordering process. A DMETS staff member wrote two different inpatient orders, each consisting of a combination of marketed and unapproved drug products and prescriptions for LidoSite. These written prescriptions were optically scanned and one prescription was delivered via email to a group of study participants. In addition, one DMETS staff member recorded a verbal inpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via e-mail.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<p>Inpatient Rx #1:</p> 	<p>Outpatient:</p> <p>Lidosite To be applied to the forearm times 1 today before the procedure</p>
<p>Inpatient Rx #2:</p> 	

2. Results:

Study	Number of participants	Number of responses (%)	"LidoSite" responses (%)	Other responses (%)
<i>Written:</i>				
Inpatient #1	43	27 (63%)	24 (89%)	3 (11%)
Inpatient #2	43	28 (65%)	26 (93%)	2 (7%)
<i>Verbal:</i>				
Outpatient	41	33 (80%)	9 (27%)	24 (73%)
Total:	127	88 (69%)	59 (67%)	29 (33%)



Among participants in the written inpatient #1 prescription study, 24 of 27 respondents (89%) interpreted the name correctly. Incorrect interpretations included Lido (1), Lidocaine (1) and Lidocanine (1).

Among participants in the written inpatient #2 prescription study, 26 of 28 respondents (93%) interpreted the name correctly. Incorrect interpretations included Lidocite (1), and Ludiosite (1).

Among participants in the verbal outpatient prescription study, 9 of 33 respondents (27%) interpreted the name correctly. Incorrect interpretations included Lidocide (1), Lidocite (14), Lidocyte (7), Litosite (1), and Lydolyte (1).

One of the misinterpreted names was Lidocaine, which is a currently marketed drug product. Lidocaine is also the principal active ingredient in the proposed product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, “LidoSite”, the primary concerns raised were related to sound-alike and look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with LidoSite were Lithostat and Lodosyn.

DMETS also conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that LidoSite could be confused with proprietary or established names known in the U.S. marketplace. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of the incorrect interpretations of the written and the verbal studies were misspelled/phonetic variations of the proposed name, LidoSite.

LidoSite and Lithostat have the potential to sound-alike when spoken. The sound-alike characteristics can be attributed to the fact that LidoSite and Lithostat contain the same number of syllables (3), and the first syllable of each name begins with the same “Li” sound and ends with the same “o” sound. Although the second syllable of each name begins with an “s”, the sound of the second syllables “Site vs. stat” when spoken aids in distinguishing the names. LidoSite and Lithostat also have a number of characteristics that aid in differentiating the products. These include the product strength (10% / 0.1% vs. 250 mg), indication for use (— vs. chronic urea-splitting urinary infections), frequency of administration (one, but may be repeated vs. 3 or 4 times a

day), route of administration (topical vs. oral), and dosage formulation (— patch vs. tablet). It also appears LidoSite may be administered by healthcare professionals prior to other medical procedures (venipuncture, IV Cannulation, etc.) and not normally dispensed to patients. However, if the product is dispensed to outpatients a health professional should thoroughly educate the patient on how to administer the medication prior to use. Although the names possess some sound-alike characteristics, the risk of dispensing the wrong medication is low based on the different product characteristics between the medications.

LidoSite and Lodosyn have the potential to sound-alike when spoken. The sound-alike characteristics can be attributed to the fact that LidoSite and Lodosyn contain the same number of syllables (3), and the first syllable of each name begins with a similar sound, "Lido vs. Lodo". Although the second syllable of each name begins with an "s", the sound of the second syllables "Site vs. syn" when spoken aids in distinguishing the names. LidoSite and Lodosyn also have a number of characteristics that aid in differentiating the products. These include the product strength (10% / 0.1% vs. 25 mg), indication for use (— vs. parkinsonism), route of administration (topical vs. oral), and dosage formulation (— patch vs. tablet). It also appears LidoSite may be administered by healthcare professionals prior to other medical procedures (venipuncture, IV Cannulation, etc.) and not normally dispensed to patients. However, if the product is dispensed to outpatients a health professional should thoroughly educate the patient on how to administer the medication prior to use. Although the names possess some sound-alike characteristics, the risk of dispensing the wrong medication is low based on the different product characteristics between the medications.

III. PACKAGING, LABELING, AND OTHER SAFETY RELATED ISSUES:

DMETS has reviewed the draft container label, carton labeling and package insert labeling in an attempt to focus on safety issues to prevent possible medication errors. The draft container label and carton labeling reviewed were dated 5 June 2003.

1. General Comments

a.

b. The NDC number appears in a different location throughout the labeling. DMETS recommends relocating the NDC number to the upper right hand corner, so it does not interfere with any text on the label.

c. The sponsor refers to their system as an — on the container label and carton labeling. —

2 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

IV. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, LidoSite.
2. DMETS recommends implementation of the labeling revisions outlined in Section III to encourage the safest possible use of this product.
3. DMETS recommends the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) consult with the CDER Labeling and Nomenclature Committee (LNC) for the proper nomenclature of the established name.
4. DDMAC found the proprietary name, "LidoSite" acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Scott Dallas, R.Ph.
Safety Evaluator
Office of Drug Safety (DMETS)

Concur:

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Scott Dallas
7/24/03 08:40:02 AM
PHARMACIST

Carol Holquist
7/24/03 08:42:35 AM
PHARMACIST

Compton, Kimberly

From: Lee, Kevin
Sent: [REDACTED]
To: Compton, Kimberly
Cc: Jani, Parinda; Rappaport, Bob A; Fogarty, Pauline J.; Lee, Kevin; Kramer, Mark; Witten, Celia; Stevens, Ted
Subject: RE: N 21-504 Vyteris Northstar lidocaine iontophoretic system

Kimberly [REDACTED] I received it on May 27, 2003. I guess that there will be no big issues.

Kevin

-----Original Message-----

From: Compton, Kimberly
Sent: Thursday, June 26, 2003 3:41 PM
To: Fogarty, Pauline J.; Lee, Kevin; Kramer, Mark
Cc: Jani, Parinda; Rappaport, Bob A
Subject: N 21-504 Vyteris Northstar lidocaine iontophoretic system

Hello,

We just wanted to let you know that we will not be able to approve this NDA in this cycle since a site inspection was not able to be completed due to the sponsor's inability to have the site ready before the goal date of July 25, 2003. We expect to send an approvable letter with deficiencies to which the sponsor will respond and be ready for inspection of their facility in the next review cycle.

We understand that the sponsor has submitted their 510(k) to you and wondered if you might provide us with the status of that submission and your review, etc., so we can keep that in our records for the next review cycle.

Thanks,
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthetic, Critical Care and
Addiction Drug Products (HFD-170)
301-827-7432

Lee, Kevin

From: Lee, Kevin
Sent: Tuesday, June 03, 2003 3:46 PM
To: Foreman, Christy
Cc: Stevens, Ted; Witten, Celia; Melkerson, Mark N.; Fogarty, Pauline J.
Subject: FW: N21-504 (Vyteris,Inc) , Northstar Iontophoretic Delivery System

Christy,
Vyteris, Inc, submitted 510(k) of the above NDA for a controller. The number is K 031551.
Thanks

Kevin

-----Original Message-----

From: Lee, Kevin
Sent: Thursday, May 22, 2003 1:28 PM
To: Stevens, Ted
Cc: Witten, Celia; Melkerson, Mark N.; Fogarty, Pauline J.; Foreman, Christy
Subject: N21-504 (Vyteris,Inc) , Northstar Iontophoretic Delivery System

Ted,
I received a consultation from CDER long time ago, but the document has become available since yesterday. The patch is part of NDA.
510(k) of the controller will be evaluated through 510(k), and was not in house yet.
In the consultation from CDER, it was requested that the facility be inspected by CDRH. I gave printed out documents and zip diskette containing the documents of the manufacturing of this device to Christy Foreman today.
Christy will sort out how to handle that inspection.

Kevin

FROM: K. Lee, M. D., Medical officer
FDA / CDRH / ODE / DGRND / REDB
SUBJECT: NDA 21504 Northstar Lidocaine iontophoretic Drug Delivery System
Vyteris, Inc.
TO: The file
Through: Chief, REDB  mp 6/10/03

Comments by K. Lee

The sponsor described manufacturing process and specifications for the iontophoretic patch, the pouch container closure, pH hydrogen surface of anode and cathode, anode specific capacity of anode and cathode, dielectrical leakage current, patch leakage current, patch conductance, hydrogel/electrical conductivity of anode and cathode, and container closure. These specifications and manufacturing process seem appropriate. The batch tests were reviewed and the test results of batch products were within the specification set by the sponsor. As far as the safety is concerned, the patch is safe to use since the current is 1.77mA (1.77/1000 coulomb/ sec) and voltage 35V. As far as the effectiveness is concerned, it should be evaluated by the CDER. I have neither deficiencies nor any issues in this submission.

K. Lee, M. D.
Medical Officer

The following is the summary of the sponsor's NDA CMC submission pertinent to the device.

Intended use

Northstar system is indicated

The Device description

The northstar patch is for one use only and disposable. This patch contains drug and return reservoirs. The 5Cm² circular drug reservoir delivers lidocaine and epinephrine to the skin where the elongated return reservoir contains electrolytes to complete the electrical circuit. The controller will flow 1.77mA for 10 minutes.

4.2.9 Method of Manufacturing and In Process Controls

A completed batch record (Lot # 0172002) representative of the iontophoretic patch manufacturing process is attached.

4.2.9.1 Brief Description of the Manufacturing Process

The iontophoretic patch manufacturing process consists of constructing the patches and individually packaging the patches in a sealed, peelable, foil/foil pouch (chevron design).

4.2.9.2 Manufacturing Instructions & In-process Controls

C

6 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

For Consulting Center Use Only: 5/24/03 data available
Date Received: 4/23/03
Assigned to: KKL / Kevin Lee, MD
Date Assigned:
Assigned by: JPS: Ted Stevens
Completed date: None 4, 2003
Reviewer Initials: Jee
Supervisory Concurrence: JPS/MJO 6/10/03
Sent 6/11/03 PR

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH
Division: DGRND
Mail Code: HFZ-410
Consulting Contact Name: Pauline Fogarty, ADPO
Building/Room #: Corp., Rm 350E
Phone #: 301-594-1184
Fax #: 301-594-2358
Email Address: PXF@cdrh.fda.gov
RPM/CSO Name and Mail Code: N/A

From (Originating Center):

Center: CDER
Division: DACCADP
Mail Code: HFD-170
Requesting Reviewer Name: Ravi Harpanhalli, Ph.D.
Requesting Reviewer's Concurring Supervisor's Name: Dale Koble, Ph.D.
Building/Room #: PKLN 9B-45
Phone #: 301-827-7440
Fax #: 301-443-7068
Email Address: harpanhalli@cdcr.fda.gov
RPM/CSO Name: Kim Compton (comptonk@cdcr.fda.gov)
(consult initiated by PJ, CPMS, 4-18-03)

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 4-14-03

Requested Completion Date: June 13, 2003

Submission/Application Number: N 21-504
(Not Barcode Number)

Submission Type: NDA-combination product
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Submission Receipt Date: 9-25-02

Official Submission Due Date: 7-25-03

Name of Product: Northstar Lidocaine Iontophoretic Drug Delivery System Name of Firm: Vyteris, Inc.

Intended Use: _____

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

The documents associated with this application are available in CDER's Electronic Document Room (EDR), accessible through the CDER Intranet. Please contact the Project Manager if you require assistance accessing these documents.

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

The iontophoretic drug delivery system has two components, the patch (including electrodes and reservoirs) and the controller. The controller is being submitted as 510(k) to CDRH and the patch is described in the NDA. It appears that there will be some overlap between the NDA and the 510(k) with regard to the electrical aspects of the patch.

46 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type): **N 21-504, Northstar Lidocaine Iontophoretic Drug Delivery System** : **mg lidocaine HCl: — mg epinephrine bitartrate)**

Applicant: **Vyteris, Inc.**

Date of Application: **9-25-02**

Date of Receipt: **9-25-02**

Date of Filing Meeting: **11-8-02**

Filing Date: **11-24-02**

Indication(s) requested:

Type of Application: Full NDA Supplement _____
(b)(1) _____ (b)(2)

[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S P _____
Resubmission after a withdrawal or refuse to file (after WD)
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) _____

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
YES NO

If the application is affected by the application integrity policy (AIP), explain. NO.

User Fee Status: Paid Waived (e.g., small business, public health) _____
Exempt (orphan, government) N/A
Form 3397 (User Fee Cover Sheet) submitted: YES: NO _____
User Fee ID# 4401
Clinical data? YES NO _____ Referenced to NDA# _____
Date clock started after UN _____

User Fee Goal date: 7-25-03

Action Goal Date (optional) _____

- Does the submission contain an accurate comprehensive index? YES NO
- Form 356h included with authorized signature? YES NO
If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- If electronic NDA, does it follow the Guidance? YES NO NA
If an electronic NDA: all certifications must be in paper and require a signature.
- If Common Technical Document, does it follow the guidance? YES NO NA
- Patent information included with authorized signature? YES NO

• Exclusivity requested? YES; If yes, _____ years NO
Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

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

Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, "To the best of my knowledge,"

- Financial Disclosure included with authorized signature? YES NO
(Forms 3454 and/or 3455)
If foreign applicant, the U.S. Agent must countersign.
- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO
If no, for what ages and/or indications was a waiver and/or deferral requested: **Deferral requested for ages 5 and under.**
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? **YES**. If not, have the Document Room make the corrections.

List referenced IND numbers: **I 48, 365**

End-of-Phase 2 Meeting? Date 9-16-99 NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s) 11-9-01 NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? **(Label available in EDR, DDMAC invited to team meetings.)**

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
Sponsor has not yet provided tradename or carton/container labeling. Once provided it will be consulted to ODS.

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
YES NO NA X

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support?
YES NO NA X

Advisory Committee Meeting needed? YES, date if known _____ NO X

Clinical

If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NO NA X

Chemistry

Did sponsor request categorical exclusion for environmental assessment? X YES NO
If no, did sponsor submit a complete environmental assessment? YES NO
If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) package submitted? X YES NO
- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO NA X

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). **This application provides for the indication of _____ at differing doses and amperages from that of the RLD.**

Name of listed drug(s) and NDA/ANDA #: **Iontocaine (N 20-530)**

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?
(Normally, FDA will refuse-to-file such applications.)

YES NO X

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?

If yes, the application must be refused for filing under 314.54(b)(1) YES NO X

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?

YES NO X

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

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

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

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

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.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

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

21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for 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.

21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference? **These issues will be addressed in the exclusivity summary checklist, to be completed at the end of the review cycle.**

YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO X

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? **An agreement was reached with the sponsor to exempt them from this requirement.**

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO X

CHEMISTRY –

- Establishment(s) ready for inspection? YES NO _____
- File Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

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

_____ The application is unsuitable for filing. Explain why:

Kimberly Compton, R. Ph., 4-7-03
Regulatory Project Manager, HFD-170

Initialed by Parinda Jani, 4-7-03
CPMS, HFD-170

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

/s/

Kimberly Compton
4/17/03 06:35:44 PM

Memo of Preliminary Issues Identified During Filing Review- Communicated to Sponsor by fax

Date: December 10, 2002

From: Kim Compton (Comptonk@cderr.fda.gov, fax # 301-443-7068, phone 301-827-7432)

To: George Baskinger, Manager, Quality Management and Regulatory Compliance for Vyteris, Inc. (fax # 201-703-2295)

Re: NDA 21-504 Northstar Lidocaine Iontophoretic Drug Delivery System

We have completed our filing review of your application and have identified the following issues:

1. As indicated during the pre-NDA meeting of November 9, 2001, publicly available data may be used to support the assessment of reproductive toxicity potential of lidocaine and epinephrine under a 505(b)(2) application. A preliminary review of the NDA submission did not identify an assessment of the reproductive toxicity potential of this drug product. This information should be provided in a timely manner to allow for adequate review of the data.
2. Provide a specification for in vitro drug release for the patch and describe the test method and its validation.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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

/s/

Kimberly Compton
12/10/02 05:07:49 PM
CSO

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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

1. APPLICANT'S NAME AND ADDRESS Vyteris, Inc. 13-01 Pollitt Drive Fair Lawn, NJ 07410	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER N021-504
2. TELEPHONE NUMBER (Include Area Code) (201) 703-2299	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME Northstar Lidocaine Iontophoretic Drug Delivery System	6. USER FEE I.D. NUMBER 4401

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

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92. (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See Item 8, reverse side if answered YES)

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

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

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

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

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE President	DATE 24 September 2002
---------------------------------------------------------------------------------------------------------------------------------------	--------------------	---------------------------

19.2 Disclosure Statement

Table 1 lists investigators who enrolled subjects into the covered clinical studies referenced above who were full-time employees of Becton Dickinson & Company at the time of the clinical investigation. Employees were compensated by salary and other agreements as a part of their employment. Financial disclosure forms were not signed by employees. Attached is Form FDA 3455 which indicates that the investigators listed in Table 1 entered into a financial agreement by being employees of the sponsor, Becton Dickinson & Company at the time of the investigation.

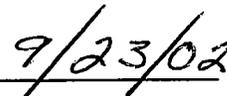
19.3 Certification Statement

Vyteris, Inc. certifies to the absence of financial interests and arrangements regarding compensation affected by the outcome of clinical studies (as defined in 21 CFR 54.2(a)), financial interests and arrangements regarding significant equity interest in the sponsor of a covered study (as defined in 21 CFR 54.2(b)), proprietary interest in the test product (as defined in 21 CFR 54.2(c)), and significant payments of other sorts (as defined in 21 CFR 54.2(f)) for clinical investigators who have enrolled subjects into the covered clinical studies referenced above and who were not employees of Becton Dickinson & Company at the time of the clinical investigation. These investigators are listed in Table 2; the investigators from whom financial information was not obtained are indicated.

Vyteris, Inc. certifies that it acted with due diligence to obtain the information required under 21 CFR 54 from all clinical investigators who have enrolled subjects in the covered clinical studies listed above and who were not employees of Beckton Dickinson & Company at the time of the clinical investigation. Attached is Form FDA 3454 with a list of clinical investigators (who were not employees of Becton Dickinson; Table 2).



Vincent De Caprio, President



Date

Vyteris, Inc.

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning See attached list (Table 1), who participated as a clinical investigator in the submitted study 98NS01-09, 98NS01-11, and BDTS-99-25, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

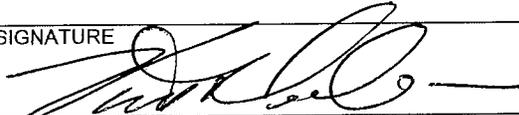
any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Vincent De Caprio	TITLE President
FIRM/ORGANIZATION Vyteris, Inc.	
SIGNATURE 	DATE 9/23/02

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

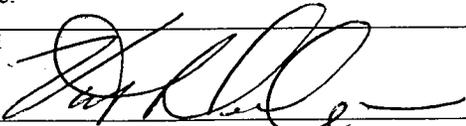
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list (Table 2)	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Vincent De Caprio	TITLE President
FIRM/ORGANIZATION Vyteris, Inc.	
SIGNATURE 	DATE 9/23/02

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Memo of CMC Issues - Communicated to Sponsor by fax

Date: 8-8-02

From: Kim Compton (Comptonk@cdcr.fda.gov, fax # 301-443-7068, phone 301-827-7432)

To: Vyteris, Inc. c/o Jim Burns of PharmaNet (fax # 609-720-5003)

Re: NDA 21-504 Northstar Lidocaine Iontophoretic Drug Delivery System

In a teleconference with the sponsor on June 28, 2002, several CMC issues were outlined for the sponsor that would require their additional follow-up. The sponsor requested we outline these issues in writing for them for clarification. These issues follow in this memo and were communicated to the sponsor by fax and email on August 16, 2002.

1. A listing of the testing and manufacturing sites is needed. Vyteris is the main site with alternatives listed. Clarification of which sites would perform which function is needed. Also, they need to provide CFN numbers for the sites. *The sponsor stated that they would provide this information.*
2. In table 4.2.6-1, clarification of which items would pertain to the 510K application and which would pertain to the NDA is needed. *The sponsor stated that the 510K would only cover the device and controller, no materials on the patch, while the NDA will include all patch materials and the solution. The sponsor plans to submit the 510K within 3 months of the action letter, but will submit an informal copy to us in the next few weeks.*
3. Samples of the system, e.g., one or two controllers and 6 (or more) active patches were requested. *The sponsor stated that they would provide these.*

**This is a representation of an electronic record that was signed electronically and
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/s/

Kimberly Compton
8/16/02 12:07:12 PM
CSO

MEMORANDUM OF TELECON

Date: June 28, 2002

Application Number: NDA 21-504

Drug: Northstar Iontophoretic lidocaine drug delivery system

Between:

— (representing the sponsor)
—
— and other representatives of the sponsor.

Sponsor: Vyteris

And:

Art Simone, M.D.
Nancy Chang, M.D.
Ravi Harapanhalli, Ph.D.
Dale Koble, Ph.D.
Kim Compton

Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170

Subject: Filing Issues

The sponsor was contacted to discuss several clinical and chemistry issues that required attention prior to filing the application.

These issues included the following:

CMC Issues-

1. A listing of the testing and manufacturing sites is needed. Vyteris is the main site with alternatives listed. Clarification of which sites would perform which function is needed. Also, they need to provide CFN numbers for the sites. *The sponsor stated that they would provide this information.*
2. In table 4.2.6-1, clarification of which items would pertain to the 510K application and which would pertain to the NDA is needed. *The sponsor stated that the 510K would only cover the device and controller, no materials on the patch, while the NDA will include all patch materials and the solution. The sponsor plans to submit the 510K within 3 months of the action letter, but will submit an informal copy to us in the next few weeks.*
3. Samples of the system, e.g., one or two controllers and 6 (or more) active patches were requested. *The sponsor stated that they would provide these.*

Clinical Issues-

After reviewing a **sampling** of the data tables, some serious errors were discovered. The Division felt that even though only some errors were detected, this might be representative of more widespread errors that were not discovered in this cursory review for fileability. Examples of these items were outlined in a memo dated 6/28/02, for the sponsor and communicated to them by fax prior to this TC (6/28/02).

Overall, the Division stated that the clinical review team did not feel the application was in compliance with the guidelines for electronic submissions. The Division stated that even if the sponsor were able to address the cited issues, we would still require evidence of thorough quality assurance of the entire application. The Division also recommended the sponsor check the application against the Guidance.

In the application's submitted format, the Division did not consider the application to be readable/interpretable. The Division informed the sponsor that they would need to decide by July 8, 2002 if the application were fileable or not. They recommended the sponsor use the remaining time before the decision was to be made to examine the application.

A follow-up TC was held with the sponsor on the filing date, July 8, 2002. A separate memo of that TC was created.

Documented by: Kim Compton, Project Manager, 8-8-02

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Kimberly Compton
8/16/02 01:02:41 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 48,365

Vyteris, Inc.

C/O: —
—
—

Attention: —
—

Dear —

Please refer to the meeting between representatives of your firm and FDA on November 9, 2001. The purpose of the meeting was to discuss the submission of your New Drug Application (NDA).

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

If you have any questions, contact me at (301) 827-7432.

Sincerely,

Kimberly A. Compton
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES

Meeting Date: November 9, 2001 **Time:** 3:30pm EST
Location: Parklawn Conference Center, Chesapeake Rm.
Sponsor: Vysteris, Inc.
IND: 48,365
Drug: Lidocaine/epinephrine Iontophoretic Device
Indication: Local anesthesia (topical)
Meeting Chair: Bob Rappaport, M.D.
Minutes Recorder: Kimberly Compton, Regulatory Project Manager

<u>FDA Attendees:</u>	<u>Titles:</u>	<u>Offices:</u>
Cynthia McCormick, M.D.	Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD-170
Nancy Chang, M.D.	Medical Officer	HFD-170
Suzanne Thornton, Ph.D.	Pharmacology/Toxicology Reviewer	HFD-170
Tim McGovern, Ph.D.	Supervisory Pharmacologist	HFD-170
Albert Chen, Ph.D.	Biopharmaceutical Reviewer	HFD-170
George Liao	Regulatory Health Information Specialist	HFD-170
Mike Theodorakis, Ph.D.	Chemistry Reviewer	HFD-170
Dale Koble, Ph.D.	Chemistry Team Leader	HFD-170
Eric Duffy, Ph.D.	ONDC II, Director	HFD-820
Kevin Lee, M.D.	Medical Officer, CDRH	HFZ-410
Stella Grosser, Ph.D.	Biostatistician	HFD-170
Tom Permutt, Ph.D.	Biostatistics Team Leader	HFD-170
Kimberly Compton	Regulatory Project Manager	HFD-170

Participants: _____ Titles: _____

Vysteris, Inc.

George Baskinger

Manager, Quality Management/Regulatory Compliance
Consultant,

Ray Garrison

Director, Manufacturing and Process Development

Cutis Karl, Ph.D.

Project Manager

Consultant

Robert Stowe

Lead Electronics Engineer

Bobby Singh

Research

Meeting Objective:

To answer the questions posed to the Agency by the sponsor in the meeting packet, intended to clarify information with regard to submission of an NDA package for this product.

General Discussion:

Dr. Rappaport opened the discussion by stating that one of the issues the Agency hoped to clarify with the sponsor was the issue of filing as a 505(b) 2 vs. 505(b) 1. He noted that regardless of which format the sponsor chose, complete information would be needed to evaluate the application.

Dr. Chang addressed the clinical issues cited in the meeting packet.

Slide 1-

- Adhesiveness/burns on CRF's
 - AE terms, details: e.g. "burning sensation", slight burn, burn, application site burning
 - Pain NOS
 - vasoconstriction
- Discrepancy in trial numbers
- Epinephrine 1 mg
 - Safety evaluation for systemic toxicity (BP, HR, ECG, PK)
 - Special populations that may be sensitive to epi: cardiovascular disease, reynaud's, sympathomimetics, beta blockers, MAOI, TCA's, COMT inhibitors, ergots, halothane, hyperthyroid, elderly, glaucoma, pregnancy, digitalis etc.

Slide 1 discussion-

- The sponsor inquired if the requested clarifications could be provided in a narrative form and Dr. Rappaport responded that whichever form the sponsor chose, it should be used consistently throughout the application. Dr. McCormick stated that the sponsor should look at derivations and spell out where those came from so searching terms would be as easy as possible for the reviewers.
- Dr. Chang noted that CRFs were requested at last meeting. She requested that the sponsor clearly define terms (like "burning sensation," etc.) and use them consistently. She further explained that care should be taken to ensure that similar adverse events should not be

categorized separately in an arbitrary manner that might “dilute” the apparent adverse event incidence. She specifically requested that the terms “Pain NOS” and “vasoconstriction” be more clearly defined, and that details of the actual signs and symptoms experienced by patients be available for review.

- Dr. Chang asked the sponsor to clarify an apparent discrepancy between tables in the meeting packet describing the numbers of patients comprising the total safety database for the proposed NDA (see slides 3 and 4).
- Dr. Chang noted that 1 mg of epinephrine is a substantial dose, both in absolute terms and also relative to other similar products on the market. It is not clear how much epinephrine is delivered out of the iontophoretic system. She concluded that data evaluating clinical safety in humans (such as by appropriate evaluations of blood pressures, heart rate, and ECG) will be required, as well as data evaluating the potential for systemic exposure to epinephrine. The sponsor stated that, theoretically, 6mcg of epinephrine is delivered, but less than that goes into the body system. Dr. Chang noted that clinically, even 5-10 mcg can lead to a significant clinical response and even if only 6 mcg is delivered (especially in special populations) that dose could be problematic. She requested that the sponsor provide full documentation of the expected delivery of epinephrine from the device. The application should also address the special populations, such as those listed on the slide, that might be particularly sensitive to exposure to epinephrine.
- Dr. Duffy stated that the Agency is looking for *in vivo* measurements, and that if the levels could not be measured, the sponsor would need to state why they believed this to be the case and provide an explanation. The sponsor inquired about a situation where the systemic level is below the level of detection of the assay. Dr. McCormick answered that the labeling would

be based on what is seen from the data. If the sponsor is unable to assess based on PK and there is not enough safety data, the sponsor may need to perform additional work. The sponsor stated that currently they have no assay for in vivo epinephrine. Dr. Duffy stated that such assays do exist. The sponsor inquired if no effect could be demonstrated and safety vitals did not change, would specific populations still need to be addressed directly. Dr. Chang stated that in any case, information about special populations, as well as special sites, etc., would be needed for the labeling. She went on to say that it would be difficult to escape any precautionary labeling in a product containing epinephrine. The sponsor stated that they were requesting a "level playing field" and did not want to be "singled-out."

Slide 2-

Combination rule (CFR 300.50)

Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy....

Slide 2 discussion-

- Dr. Chang noted that there are safety issues for both ingredients in this product. The regulation cited above is generally interpreted that the sponsor must demonstrate that each component contributes more than each alone. Dr. Chang noted that this issue will soon be presented to the Medical Policy Coordinating Committee (MPCC) and so further information on this policy and its implications may follow. The sponsor noted that they have 2 (not pivotal) phase 1 studies that demonstrate the contributions of both ingredients with the prototype device. Dr. Duffy noted that the sponsor should give a clear description of the differences between the prototype device and the to-be-marketed (TBM) product. Dr. McCormick

requested that the sponsor point out these studies to the Agency and we would review them briefly to see if they were acceptable. She requested the sponsor draft and send the Division a synopsis (less than 1 page) of the study designs and why the sponsor feels these address the combination issue. The sponsor indicated that they would be able to generate such synopses and submit them as amendments.

Slide 3-

Slide 3 is a copy of "Table 1 Summary of Treatments" from the meeting packet.

Slide 3 discussion-

- Dr. Chang requested that the sponsor clarify the apparent discrepancy in the table. The sponsor stated that some studies could not be pooled so there are different numbers in the totals. The sponsor state that this was explained in the ISS.

Slide 4-

Slide 4 is a copy of "Table 2 Subject Disposition" from the meeting packet.

Slide 5-

- Electrical safety: pacers, fibrillation, isolated circuit, ignition source, user control over current flow (skin impedance)
- Application sites - e.g. mucous membranes, temporal/orbital regions, digits
- Intermittent incomplete contact with skin

Slide 5 discussion-

Dr. Chang requested that the sponsor please address the issues listed under "Electrical safety," and that they define appropriate sites as mentioned under "Application sites." Dr. Chang inquired if intermittent incomplete contact with skin would be a source of burns. The Division would like an understanding of the magnitude and method(s) of monitoring such adverse events and the ways these adverse events might be prevented.

At this point the sponsor re-visited the epinephrine issue. The sponsor felt that getting blood levels of epinephrine was not feasible. They stated that they could analyze used patches and see how much epinephrine is left and therefore state how much is delivered. Dr. Duffy stated that based on analytical variability the suggested measurement plan does not seem useful. Dr. McCormick stated that the sponsor may find that the clinical safety data is the only way to address this issue.

Dr. Thornton addressed the Pharm/tox questions from the packet.

Slide 6-

Q1. *Does the division accept the request for a waiver from the need to conduct reproductive toxicology studies?*

A1. 505(b)(1)

- must conduct the reproductive toxicology studies (due to systemic exposure to lidocaine)
- clinical PK study will determine if the studies will be needed for the combination product or lidocaine alone

505(b)(2)

- reproductive toxicology studies waived
- use available supporting data for lidocaine and epinephrine

Slide 6 discussion-

Dr. Thornton stated in reference to the “clinical PK” information that if the sponsor can measure systemic exposure levels greater than background levels the sponsor will need to perform reproductive toxicology studies on both ingredients. The sponsor inquired what an acceptable level was. Dr. McCormick stated that the sponsor should make their case to the Agency regarding what level is acceptable with appropriate justification for not needing to perform these studies. The Division will consider the sponsor’s rationale. Dr. Chang stated that this is another reason to provide clinical safety information.

Slide 7-

Q2. *Is the non-clinical toxicology plan acceptable for an NDA?*

A2. 505(b)(1)

Studies already conducted:

- lidocaine/epinephrine - local irritation/sensitization studies, 14-day repeat-dose study in rabbits
- lidocaine alone - genotoxicity, skin irritation studies

Studies required with lidocaine/epinephrine:

- 1-month repeat-dose study in two species (according to ICH-M3 Guidance); or
- submit rationale and supporting evidence as to why these studies are not necessary to conduct

Slide 7 discussion-

In reference to the ICH-M3 Guidance mentioned in this slide, Dr. Thornton elaborated that such studies would include full toxicology, systemic exposure, and PK. Dr. Thornton reminded the sponsor that information submitted but not owned by the sponsor must be in the public domain.

Dr. McCormick stated that the sponsor should be careful about what they reference and who owns the data. Dr. McGovern stated that a request for a waiver for the toxicity studies under a 505(b)(1) application should be based on the long history of safe use of the product in humans as it would be difficult to support using nonclinical data from the published literature.

Slide 8-

Q2. *Is the non-clinical toxicology plan acceptable for an NDA?*

A2. 505(b)(2)

- no further studies required
- use available supporting data for lidocaine and epinephrine

At this point the sponsor inquired about possible exclusivity terms. Dr. Rappaport stated that the potential for exclusivity with this application would be 3 years if no other similar product were approved first.

Dr. Theodorakis addressed the CMC issues in the packet.

Slide 9-

Q1. Do the stability data to be presented in the NDA justify a 2- year shelf life?

A1. No. You have provided only pivotal (primary) stability data for the drug product stored at 25°C/60% RH. We need to see the data on the three lots. At that time we will also consider the 24 month supportive data

Slide 9 discussion-

The sponsor stated that they expect stability data at filing, while only is required. Dr. Theodorakis stated that the sponsor may submit updated stability information as an amendment after the application is filed.

Slide 10-

Q2. Does the FDA agree that a is justified by the data?

A2. Provisionally this is acceptable.

Slide 10 discussion-

Dr. Duffy inquired why both products

Slide 11-

Q3. Does the unique iontophoretic drug delivery system, including the , justify a label claim of of the theoretical ' mg lidocaine hydrochloride and mg epinephrine?

A3. We prefer to maintain the acceptance criteria for the assay within

Slide 11 discussion-

Dr. Theodorakis stated that the Agency wants to review the data for this issue and then can decide. Dr. Duffy stated that perhaps the more appropriate expiration date is — , not 24 months. Dr. Koble stated that both requests are generally unacceptable, so the sponsor would need to clearly make the argument for why they believe these limits should be accepted and then the Agency will review the argument. Dr. Duffy stated that our decision on this issue would be data driven.

Slide 12-

- The degradation products should be individually expressed in terms of % D[rug].S[substance]. as well as in terms of amount per patch.
- Provide appropriate justification of the acceptance criterion for the Probe Tack Test (i.e., analysis of data from lots used in the clinical studies).
- Provide a specification for in vitro release test for the drug product.

Slide 12 discussion-

The sponsor stated that they have done some work on an *in-vitro* release test and they have a summary of it, but that they feel drug release testing can be controlled by the patch-chemical and physical tests. Dr. Duffy stated that the Agency feels this added test is important since it is a performance measure. The sponsor stated that they plan to address that in the NDA but have not yet been successful in such tests. Dr. Duffy stated that the Agency realized this test may be difficult and the technological obstacles exist, but that the effort is expected to be made and noted that the Agency may request this as a post-marketing commitment if it is not accomplished before the NDA process. The sponsor indicated that they may have success with lidocaine, but not with epinephrine. Dr. Koble stated that if exceptions exist the Agency will consider the situation but that we feel the product should have this test and that it is able to be accomplished. Dr. Koble questioned what data could be provided to support adequate drug release through shelf life and

indicated that the sponsor should include the age of the batches used in the clinical trials in the submission.

Dr. Lee from CDRH presented some information.

Slide 13-

- Include device specification information in the NDA (similar to that which was provided in Amendment 11 to the IND.)
- Include information on hazard evaluation and working mode of the microprocessor.
- Specify whether the microchip of the controller can regulate the constant current in the change of skin resistance.

Slide 13 discussion-

Dr. Lee provided a list of information to be requested from the sponsor and asked that it be provided with the minutes of this meeting. The list is attached as item #1.

Follow-up discussion-

The sponsor stated that the information Dr. Lee requested would be included in the 510K application. Dr. Lee stated that the 510K cannot be approved before the NDA is approved, and therefore requested that the sponsor submit the 510K approximately 50- 90 days prior to the action of the NDA. Dr. McCormick stated that the sponsor could send the requested device information in unofficially with the NDA for Dr. Lee to review, then submit the official 510K application in the 90 days prior to the NDA action.

Further Discussion-

The sponsor inquired if this application would require an Advisory Committee. Dr. Rappaport indicated that at this point, the Division did not know.

The sponsor indicated that they are planning to submit the application electronically.

Dr. McCormick inquired if the sponsor had considered a pediatric plan yet. The sponsor responded that one of the pivotal studies is a pediatric study and they feel it is robust. Dr. McCormick stated that the sponsor would need to get substantial exposure in all age ranges to get pediatric labeling. She suggested that the sponsor should determine where their product fits into the treatment arena, which ages it could be used in, and which ages a waiver could be requested for. She went on to state that the sponsor could submit a waiver request for certain age ranges and/or request to defer some studies until a later time (i.e., < 5 yr. old). She also stated that the sponsor should separate out any patients under 16 years old by category in the ISS. The sponsor inquired if the age range for "child" is defined as 2-6 years old, and they have data for 5 and 6 year olds, does that suffice. Dr. McCormick indicated that it did not. She went on to state that the sponsor should consider the lowest age group that could benefit from this product and study them. She stated that the sponsor currently has enough information to file the application, but still have a portion of the patient population not studied and so will need to consider how to handle that. Dr. McCormick stated that the sponsor should put their proposals in writing and the Agency will consider them.

The sponsor summarized their understanding of the Division's position by stating that the Division's concerns seem to center around the systemic safety of epinephrine and that the Division is asking the sponsor to either measure that level systemically, or if it cannot be measured, to demonstrate clinical safety.

Action Items:

The Agency will send the official minutes of the meeting to the applicant.

Minutes prepared by: Kimberly Compton

Attachment-Item #1

Date: November 9, 2001
From: K. Lee, M.D., Medical Officer
FDA/CDRH/ODE/DGRD/REDB
Subject: IND 48,365
To: The file

I need the following information.

1. The specification of printed circuit or microprocessor with its error limit, and controller working mode
2. Microprocessor software if applicable
 - a. Hazard analysis
 - b. Verification and validation
3. The allowable tolerance of microprocessor and its safety guard
4. Current and voltage, with its error limit and the duration of iontophoresis application
5. Active surface area and current density of each electrode
The current dose must be specified in each study and expressed by _ current density (mA/cm²)
x _ minutes.
6. The composition, dimension, and construction of each electrode
7. Prescription label on the device
There should be statement on the device and label "Caution: Federal law restricts this device to sale by or on the order of a _____, the blank to be filled word "physician," "dentist," or with any other practitioner licensed by the law of the state (21CFR801.109)
8. Device manual
9. The sponsor will also provide dermal irritation data at allowable pH.
10. The sponsor should tabulate the current density, duration of iontophoresis, maximum voltage, active surface of the electrodes.
11. Total degradation test, appearance test, and patch adherence test of electrode should be included for stability test.
stability test:
 - the measurement of patch leakage current,
 - patch conductance test,
 - patch — description,
 - method for measuring drug release from an iontophoretic patch
 - leachables,
 - Patch pH description
12. Intended use

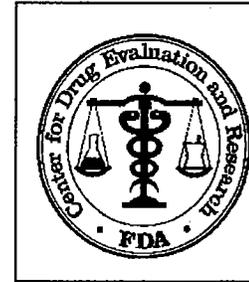
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kimberly Compton
2/21/02 03:16:05 PM

MEETING MINUTES**Meeting Date:** [REDACTED] **Time:** 1:00-2:00 p.m.**Location:** Parklawn Building, 3rd Floor, Potomac Room

[REDACTED] (lidocaine/epinephrine iontophoretic drug delivery system)

Indication: _____**Sponsor:** Becton Dickinson Transdermal Systems**Type of Meeting:** [REDACTED]**Meeting Chair:** Bob Rappaport, M.D., Deputy Director**Minutes Recorder:** Debbie Fong, Pharm.D., Regulatory Project Manager

FDA Attendees:	Titles:	Offices:
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD 170
Kim Dettelbach, J.D.	Associate Chief Counsel, Office of General Counsel	GCF-1
Harold Blatt, D.D.S.	Medical Officer	HFD-170
Albinus D'Sa, Ph.D.	Chemistry Team Leader	HFD-170
Michael C. Theodorakis	Chemistry Reviewer	HFD-170
Lucy Jean, Ph.D.	Pharmacology Team Leader	HFD-170
Anwar Goheer, Ph.D.	Pharmacology Reviewer	HFD-170
Ramana Uppoor, Ph.D.	Clinical Pharmacology & Biopharmaceutics Team Leader	HFD-870
Shinja Kim, Ph.D.	Clinical Pharmacology & Biopharmaceutics Reviewer	HFD-870
Debbie Fong, Pharm.D.	Regulatory Project Manager	HFD-170
Kevin Lee, M.D.	Medical Officer, Center for Devices and Radiological Health	HFZ-410

Becton Dickinson's Attendees:	Titles:
Seymour I. Schlager, M.D., J.D., Ph.D.	Worldwide Medical Director
Michael Gross, Ph.D.	Director, Corporate Regulatory Affairs
David W. Eaker, Ph.D., DABT	Manager, Biological Sciences, Worldwide Medical Toxicology
Sally Ann Daly	Clinical
Bruce Eliash, Ph.D.	Development
_____	Consult Statistician

Meeting Objective: The primary objective of this meeting was to respond to the firm's December 15, 1999 request to continue our discussion of End-of-Phase 2 issues, including the safety of proceeding to Phase 3, the Phase 3 clinical development plan, nonclinical toxicology plans, requirements for product comparability, CMC requirements, and other NDA requirements. Their proposed indication _____

Meeting Discussion:

Following introductions, Debbie Fong presented the agenda (Attachment 1). She initiated discussion on the order of agenda items per the sponsor's request, and informed the sponsor that we would first address regulatory/Office of General Counsel issues, since Ms. Dettelbach had to leave the meeting early. Dr. Rappaport suggested that we proceed according to the agenda as presented. He informed the sponsor that we should be able to resolve the CMC and pharmacology/toxicology issues in a timely fashion, so that we would be able to focus the bulk of our discussion, as necessary, on clinical/development plan issues. It was also emphasized that specific protocol comments would not be provided at the meeting, since we do not have final protocols at this time. However, the discussion would include comments on the general clinical development plan.

c
j

McCormick reiterated Dr. Rappaport's suggestion that we proceed with a pharmacology/toxicology discussion.

v. Dr.

Dr. Goheer reviewed the sponsor's proposed NDA studies and the Agency's recommendations related to the studies (see Attachment 2). Dr. Goheer informed the sponsor that histopathology of all dermal application sites should be done for the repeat-application primary dermal irritation study in rabbits. The sponsor indicated that this study was set up to evaluate the product in the worst clinical setting, and therefore they did not feel it was necessary to evaluate histopathology of all dermal application sites. Dr. McCormick requested that the sponsor submit their justification in writing.

Dr. Goheer stated that the primary dermal irritation study should be conducted at both low and high extremes of product pH range (i.e. pH 3 and pH 9). The sponsor stated that the product specifications are for a pH range of — i.e. pH 9 is not within the specification range. Dr. D'Sa stated that the pH increases if there is only 10% contact of the patch with the skin, and the sponsor stated that the pH does not go above pH 6. The Agency agreed that the maximum pH observed in patches with partial contact of the cathode with the skin should be studied.

Dr. Goheer stated that the Buehler dermal sensitization study outline is acceptable as proposed. He advised the sponsor that the genotoxicity (mutagenicity) studies be conducted in accordance with ICH guidelines. He then reviewed the required reproductive toxicity studies.

The sponsor stated that they do not see the reproductive toxicity studies as relevant, in the context of the targeted exposure to the patch. Dr. Goheer responded that medical literature indicates there is some systemic exposure. Even though such exposure is low, it is not known what effects such exposure would have on fetal toxicity. The sponsor inquired if there is an established limit of exposure for determining whether or not such studies are required. Drs. Rappaport and Jean responded that no such limitations are placed for a new product. The sponsor asked how a complete absence of systemic exposure can be proven. Dr. Jean asked if the sponsor has any data that there is absolutely no absorption. Dr. McCormick reinforced that data are required before we can make any assessment. Dr. Uppoor stated that, at this point, even with the most sensitive assay, the systemic levels and effects have not been established, because of the way the previous pharmacokinetic study was conducted. The sponsor stated that, from their past experience, plasma concentrations did not increase beyond 6 ng/mL. The sponsor will consider this issue and prepare their response. The sponsor asked if we have considered the potential impact such a requirement would have on other lidocaine products. Dr. McCormick stated that other companies will either have to conduct their own studies or certify to Becton-Dickinson's studies. The sponsor inquired if it would be acceptable if a repeat-dose study was conducted via another route of administration, e.g. the intravenous route. Dr. Rappaport answered that this would be acceptable, if there is a correlation of plasma concentrations with actual exposure, which can be reproduced by another route of administration. Dr. Jean stated that repeat administrations with the subcutaneous route would be acceptable to identify reproductive hazards. The toxicokinetic data from the reproductive studies can be used in human risk assessment by comparing to the human pharmacokinetic data.

Dr. Goheer again reviewed the reproductive toxicity studies in detail. The study of fertility and early embryonic development to implantation, in one species, would provide Segment I data. The study for effects on prenatal and postnatal development, including maternal function, in one species, would provide Segment III data. The study for effects on embryo-fetal development, in two species, would provide Segment II data. The sponsor pointed out that the 505(b)(1) vs. 505(b)(2) issue rests primarily on this requirement.

Dr. Goheer informed the sponsor that, in general, carcinogenicity studies are not required for local anesthetics intended for occasional use. He also confirmed that 2,6-xylylidine carcinogenicity data is considered to be in the public domain. However, the CDER Executive Carcinogenicity Assessment Committee, after reviewing relevant data, concluded that the carcinogenicity of 2,6-xylylidine is not relevant and does not need to be included in labeling.

Dr. McCormick stated that we will look into the requirements for evaluating epinephrine, and we will provide them with additional information in the near future.

The sponsor inquired what impact would result if there are undetectable concentrations of lidocaine in the blood. They acknowledged that the past pharmacokinetic studies were flawed (i.e. contamination issue), and they plan to repeat these studies. Dr. McCormick stated that the sponsor will have to explain why one set of studies demonstrated detectable concentrations of lidocaine, while another set of studies did not. Dr. Rappaport advised the sponsor to submit the results from the new studies. If the discussion must take place at a higher level within the Agency, they could pursue that route if necessary. He emphasized that we cannot grant them a waiver at this point. Dr. McCormick informed the sponsor that can apply for a waiver when they submit their NDA. Dr. Uppoor stated that the sponsor should specify the assay sensitivity, as well.

Dr. Theodorakis reviewed the CMC requirements (Attachment 3), related to the adhesiveness test, pH change, degradation products, pilot and commercial patch manufacture sameness and product comparability, post-approval changes, and presentation units for controller-patch electrical specifications.

The sponsor stated that they will record other epinephrine degradation products, including record _____ They will not record _____ Dr. McCormick requested that the sponsor submit this proposal formally for our review. Dr. Uppoor stated that, if the pilot and commercial-scale products are considered comparable upon review, then there is no need for a bioequivalence study. The sensitivity of the product, i.e. drug delivery, to the manufacturing process must be addressed. Again, this is dependent upon the NDA review. No concrete conclusions, regarding sensitivity or lack thereof, can be made at this time.

Dr. Blatt stated that the sponsor's overall Phase 3 development plan is acceptable. _____

_____ Dr. Blatt pointed out that the sponsor should seek to enroll patients with various skin types, as well as geriatric patients. The robustness of their data will determine how their product is labeled. Dr. McCormick stated that the number of patients studied is important. The sponsor should enroll and study the target age groups, to obtain as much relevant information as possible.

Dr. Lee reviewed the provisions of the sponsor's submission, amendment 11 to IND 48,365. The sponsor verified that the current area of gel contacting the skin in both the anode and cathode areas remains unchanged from that specified in amendment 11. The sponsor also confirmed that the current and charge applied, the ramp-up and ramp-down, remain unchanged. Dr. Lee concurred with the sponsor that monitoring the actual current applied to patients is not practical. Safety monitoring should be ensured, however. We agreed that safety data from studies in which the MIP2 and MIP3 patches were applied could be combined with safety data from patients enrolled in the Phase 3 studies, to establish their safety database for labeling purposes.

Dr. McCormick stated that the sponsor needs to submit their final protocols when available, for a thorough review and our specific comments. We agreed that the sponsor could conduct studies in pediatric patients under the age of 5 as a Phase 4 commitment, _____

_____ Dr. Rappaport informed the sponsor that their general development plan looks acceptable. He advised the sponsor to indicate their planned timeframe for starting these studies.

Dr. Rappaport adjourned the meeting at approximately 2 p.m.

Action Items:

1. We will issue a copy of the official meeting minutes to the sponsor.
2. The sponsor will respond to our request for reproductive toxicity study data.
3. We will look into the requirements for evaluating epinephrine, and we will provide them with additional information in the near future.
4. The sponsor will submit their final protocols when available, for a thorough review and our specific comments.

Minutes prepared by: Debbie Fong, Pharm.D.

Minutes concurred by Chair: Bob Rappaport, M.D.

CC: IND 48,365
HFD-170/Division Files
HFD-170/D. Fong/C. Schumaker
HFD-102/J. Jenkins
HFD-170/C. McCormick
 B. Rappaport
 H. Blatt/2-26-00
 A. D'Sa
 M. Theodorakis
 D. Jean
 A. Goheer/2-28-00
 S. Grosser
 T. Permutt
HFD-870/R. Uppoor
 S. Kim/2-28-00
HFD-940/A. Hussain
HFZ-410/K. Lee/2-28-00
GCF-1/K. Dettelbach/2-28-00

Drafted by: D. Fong 2/23/00
Revised: C. Schumaker/2-28-00
 R.Uppoor/3-1-00
 K.Dettelbach/3-1-00
 M.Theodorakis/3-1-00
 A.D'Sa/3-1-00
 L. Jean/3-1-00
 C.McCormick/3-1-00

Filename: 48365 (BD) EOP2MM2 2-17-00.doc



DEPARTMENT OF HEALTH & HUMAN SERVICES

Fong

Food and Drug Administration
Rockville MD 20857

IND 48,365

Becton Dickinson and Company
One Becton Drive
Franklin Lakes, New Jersey 07417

Attention: Michael Gross, Ph.D.
Director, Corporate Regulatory Affairs

Dear Dr. Gross:

Please refer to the meeting between representatives of your firm and FDA [REDACTED]. The purpose of the meeting was to discuss [REDACTED] for the Northstar System (prefilled lidocaine/epinephrine drug delivery system) for [REDACTED].

As requested, a copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact Debbie Fong, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

IND 48,365 Northstar System (End of Phase 2 Meeting Minutes)
Page 2

cc: Original IND 48,365
HFD-170/Division Files
HFD-170/D. Fong
HFD-102/J. Jenkins
HFD-170/ C. McCormick

B. Rappaport
H. Blatt
A. D'Sa
M. Theodorakis
D. Jean
A. Goheer
S. Grosser
T. Permutt

HFD-870 R. Uppoor
S. Doddapaneni
S. Kim

HFD-940/A. Hussain
HFZ-410/K. Lee

Drafted by: D.Fong 10/15/99

Initialed by: C.P. Moody 10/15/99

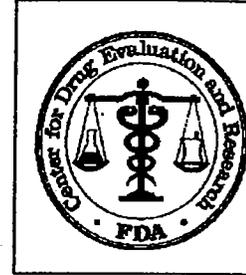
Final:

filename: 48365 (BD) MMLTR 101599.doc

End of Phase 2 Meeting Minutes

MEETING MINUTES

Meeting Date: September 16, 1999 **Time:** 3:00-4:30 p.m.
Location: Parklawn Building, 3rd Floor, Conference room K
IND: 48,365
Drug: Northstar System (prefilled lidocaine/epinephrine drug delivery system)
Indication: _____



Sponsor: Becton Dickinson Transdermal Systems
Type of Meeting: End of Phase 2 Meeting
Meeting Chair: Bob Rappaport, M.D., Deputy Director
Minutes Recorder: Debbie Fong, Pharm.D., Regulatory Project Manager

<u>FDA Attendees:</u>	<u>Titles:</u>	<u>Offices:</u>
John Jenkins, M.D.	Director, Office of Drug Evaluation II	HFD-102
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD 170
Harold Blatt, D.D.S.	Medical Officer	HFD-170
Carole Freeland, M.D.	Medical Officer	HFD-170
Albinus D'Sa, Ph.D.	Chemistry Team Leader	HFD-170
Michael C. Theodorakis	Chemistry Reviewer	HFD-170
Lucy Jean, Ph.D.	Pharmacology Team Leader	HFD-170
Anwar Goheer, Ph.D.	Pharmacology Reviewer	HFD-170
Suresh Doddapaneni, Ph.D.	Biopharmaceutics Reviewer	HFD-870
Shinja Kim, Ph.D.	Biopharmaceutics Reviewer	HFD-870
Stella Grosser, Ph.D.	Biostatistics Reviewer	HFD-170
Debbie Fong, Pharm.D.	Regulatory Project Manager	HFD-170
Ajaz Hussain, Ph.D.	Director, Division of Product Quality and Research	HFD-940
Kevin Lee, M.D.	Medical Officer, Center for Devices and Radiological Health	HFZ-410

<u>Becton Dickinson's Attendees:</u>	<u>Titles:</u>
Seymour I. Schlager, M.D., J.D., Ph.D.	Worldwide Medical Director
Michael Gross, Ph.D.	Director, Corporate Regulatory Affairs
David W. Eaker, Ph.D., DABT	Manager, Biological Sciences, Worldwide Medical Toxicology
George M. Baskinger	Regulatory Compliance
Kevin Carey	Project Management
Sally Ann Daly	Clinical
Aileen Gilbert	Regulatory Affairs
Uday Jain, Ph.D.	Pharmaceutics
	Biostatistics/CRO Consultant
	Biostatistics/CRO Consultant
Anthony Kosinski	Business Leader
Vilambi Reddy, Ph.D.	Director, Product Development

Meeting Objective: The primary objective of this meeting was to respond to the firm's request to discuss End of Phase 2 issues, including the safety of proceeding to Phase 3, the Phase 3 clinical development plan, preclinical toxicology plans, requirements for product comparability, CMC requirements, and other NDA requirements. Their proposed indication

Meeting Discussion:

Following introductions, Debbie Fong presented the agenda (Attachment 1). She began the discussion by clarifying that an in vivo demonstration of bioequivalence will not be necessary to establish comparability between pilot and commercial product, since no changes in the manufacturing process and formulation are anticipated during scale-up. Dr. Gross stated that an in-house process is in place for the manufacture of clinical and stability supplies of the pilot product. An _____ will be established to support comparability of processes. Based on their logistical plan, the sponsor will utilize a commercial process to manufacture clinical supplies. Initially, they had planned to use product manufactured by the _____ process in their clinical and stability studies, however now they plan to use the product manufactured by the commercial process also for the clinical and stability studies.

Dr. Doddapaneni stated that the sponsor's questions regarding post-approval changes should be discussed at a later date. Dr. Theodorakis stated that, in a previous meeting, the Agency and the sponsor had agreed to address post-approval changes only after approval was granted. Dr. D'Sa stated that a wide variety of post-approval changes are possible, therefore at this time, the Division cannot assert whether or not a demonstration of bioequivalence will be required. Dr. Rappaport suggested that the sponsor submit such inquiries in writing. These questions will be most appropriately discussed at their pre-NDA meeting.

Debbie Fong reviewed the sponsor's requirements for submitting a 505(b)(2) application, including the following:

- Form 356h with correctly checked box specifying that the NDA is being submitted under 505(b)(2) of the FD&C Act
- Identification of listed drug(s)
- Patent certification for listed drug(s)
- Period of marketing exclusivity on listed drug(s)
- Patent information on the sponsor's drug or use of the sponsor's drug
- Period of marketing exclusivity to which the sponsor believes they are entitled, if their NDA is approved
- Listing of studies that the sponsor will conduct in support of the NDA
- Listing of studies on which the sponsor will rely, for which primary data/right of reference is not available

Note: A relative bioavailability study comparing the proposed drug to the listed drug is generally required, however the sponsor may request a waiver of this requirement.

Dr. Goheer informed the sponsor that reproductive toxicity, irritation, mutagenicity, and carcinogenicity studies will be required. If the sponsor does not wish to repeat reproductive toxicity, mutagenicity, and carcinogenicity studies that have already been conducted by others, then they must submit their application as a 505(b)(2) application. Dr. McCormick stated that chronic

toxicity or acute toxicity studies must be performed. The sponsor may cite the literature available, or request a waiver of those studies. We would probably waive the requirement to conduct the acute toxicity studies. Dr. Gross stated that there is carcinogenicity labeling of lidocaine for some products. He asked for clarification of what type of information is considered to be public domain. Dr. McCormick stated that we can check with the Office of General Counsel.

Dr. Gross stated that a full NDA is preferable to a 505(b)(2) application for them. The sponsor may conduct other pharmacology/toxicology studies to make the application a full NDA. Dr. McCormick asked the sponsor how their proposed product is different from existing products. Dr. Gross stated that they were not prepared to discuss that at this meeting, however they will submit that information to the Division. The sponsor's proposed product is identical to existing products in indication.

Dr. Jean stated that there are no carcinogenicity studies on lidocaine to her knowledge. Currently, there are three lidocaine products containing the carcinogenicity data on 2,6-xylylidine, an intermediate metabolite of lidocaine, in the label. Based on the subsequent FDA-generated data from human liver slices and human exposure data, the Carcinogenicity Assessment Committee concluded that the extent of exposure to this intermediate metabolite was low and recommended that the carcinogenicity data of 2,6-xylylidine not be included in the label of lidocaine products.

Sponsor Presentation: Dr. Gross presented background information on the Northstar System (Attachment 2) and briefed the attendees on previous meetings and a site visit. He stated that they plan to request a pre-NDA meeting to be scheduled in the early to middle months of next year. He stated that although the Northstar System is being regulated more as a drug, it has evolved more as a device. Epinephrine was included as an active placebo group in studies to produce sensation and blanching of the skin to maintain the study blind.

Meeting Discussion (continued):

Dr. D'Sa stated that he would like the sponsor to conduct an appearance test () and an identity test. The sponsor should also conduct a functionality test for adhesiveness. A tack test may be conducted. However, a comprehensive adhesiveness test is required, due to the potential for burns resulting from non-uniform contact of the system with the skin. The sponsor should look at adhesiveness of the final configuration, therefore such tests should be conducted on the full-size patch (finished product) and stability lots.

Dr. Goheer stated that the sponsor should submit their protocols for irritation studies. Histopathology of the application site is required. He emphasized that if the sponsor intends to submit a 505(b)(1) application, their requirements will change. Dr. Gross reiterated that they require clarification on which studies are indeed needed for submission of a 505(b)(1) application, and what information is in the public domain. Dr. McCormick stated that we will have to evaluate their requirements for the epinephrine component of the proposed system.

Dr. Kim stated that one clinical study evaluated blood lidocaine concentrations. In Study 98NSO-108, 13 volunteers had blood samples taken at six different timepoints. Blood samples from three patients yielded concentrations higher than the limit of detection. In particular, one patient demonstrated high concentrations, which the sponsor attributed to contamination. When three more volunteers were studied, two of those volunteers had blood concentrations greater than the limit of detection. Dr. Kim emphasized that it is unclear if contamination is actually the cause. She presented a slide illustrating how the blood concentrations obtained from local sites continued

to increase with time (Attachment 3). However, if contamination did indeed occur, such concentrations would be expected to decrease with time. Dr. Schlager stated that this issue may be resolved in the pediatric study. He stated that all patients with blood lidocaine concentrations greater than the limit of detection had their samples obtained from local sites. This recurred in the second study. However, Dr. Doddapaneni contended that this still does not explain Dr. Kim's findings. He stated that the sponsor will need to obtain more data from their Phase 3 studies.

Dr. Gross stated that the Phase 3 studies were not designed as pharmacokinetic studies. To ask enrolled patients for an additional blood sample is not acceptable. He stated that at the pre-IND meeting, they had stated they did not plan to conduct pharmacokinetic studies, since the pharmacokinetic profiles of the drugs are already established. Dr. McCormick stated that the sponsor still needs to explain Dr. Kim's findings. An additional blood sample requirement is not unreasonable. She requested that the sponsor consider obtaining pharmacokinetic samples in their Phase 3 studies. Dr. Gross inquired if it would be acceptable to obtain one sample from each subject, conducting sampling of some patients at 0.5 hour, some at 1.0 hour, some at 2.0 hours, etc. Dr. Doddapaneni agreed that that is acceptable if approximately 50 subjects are studied. The sponsor's only alternative is to conduct another pharmacokinetic study in adults. The sponsor asked if data from the pediatric study is acceptable. Dr. McCormick stated that that is not acceptable, since pediatric patients exhibit different pharmacokinetic profiles than adults.

Dr. Kim asked if the Northstar System will be reapplied to patients who require repeat procedures. Dr. Gross stated that he did not believe that one procedure will require more than one exposure. There should be no more than two exposures per event. Dr. Rappaport contended that realistically, repeated exposures may be required, and the labeling will have to express the limitations of what has been studied.

Dr. Hussain asked the sponsor if they have monitored for a change in pH in the electrodes of the system. The sponsor stated that such a change in pH should not be observed. When they previously measured the pH of gels, no differences were observed. The —
— in the formulation should prevent pH fluctuations. Dr. Hussain inquired about pH shifts upon accidental lifting of the patch. The sponsor stated that a pH shift up to 9 (normal pH 5) was observed. Dr. Hussain expressed his concern that we do not know if —
sufficient to prevent pH changes.

Dr. Lee asked the sponsor to describe the specifications of the system when they submit their protocols/NDA, including the following: current, voltage, duration, and current density times duration (in minutes). He reminded the sponsor that the labeling of the device must be in accordance with the regulations. We agreed to provide these requirements in writing and review them in the pre-NDA meeting. The sponsor stated they have problems expressing the current density as requested. Drug delivery is based on charge. Dr. Lee stated that he was concerned about the safety of the product. The sponsor stated that drug is administered to a fixed area over a fixed time period, therefore there is no variability in administration. A 17 mA charge is controlled and delivered identically each time the system is administered, with a ramp-up and ramp-down. Dr. Hussain reiterated that if there is patch lift, then the current density is affected, and that data should be captured.

Dr. Blatt asked the sponsor to clarify if their proposed claim is —
/

Dr. Gross stated that pivotal studies will analyze the effects in cannulation in pediatric and adult patients. These will be submitted in the NDA. Other non-pivotal studies to supplement the cannulation studies are planned. A Phase 1 study to analyze the depth of analgesia achieved is planned. He inquired if the results from these non-pivotal studies are acceptable if they are not statistically significant. Dr. McCormick emphasized that anything that is included in labeling must be based on statistically significant results. She recommended that the sponsor reevaluate their plan and submit a new proposal.

Dr. Blatt informed the sponsor that in the Phase 1 study, all patients should be seen in person at 24 hours. Follow-up should be performed beyond 24 hours if there are signs of dermal burn, irritation, or other adverse events. We would like to see at least 1000 patients administered the MIPs or final patch formulation for an adequate safety database. The sponsor stated that the only difference between the MIP2 and MIP3 patches is the — Dr. Rappaport asked the sponsor to provide documentation in writing to this effect, including their available safety database. The sponsor asked if we require 1000 patients or 1000 treatments. The sponsor was informed that they should study 1000 patients. Dr. McCormick stated that the sponsor should ensure a diversified patient population, including different skin types, races, and ages.

Dr. Blatt recommended that the sponsor consider studying pediatric patients under the age of 5. The sponsor stated that this poses a problem, —

— We need to see the results of studies of children and even newborns. She asserted that we cannot waive the requirement. Such studies could be done as post-marketing studies, —

— Dr. Gross stated that there may be pediatric exclusivity issues.

Dr. Blatt also recommended that the sponsor study geriatric patients to obtain adequate safety data for the general population. Such patients should be included in Phase 3 studies. The sponsor suggested that they alternatively study geriatric volunteers, since there are few differences between patients and volunteers in this case. Dr. McCormick suggested that they include geriatric patients in the other planned studies.

Dr. Blatt stated that the sponsor should study the adhesiveness on different skin types and document adhesiveness in a field on the case report forms for correlation with adverse events. —

Dr. Rappaport asked the sponsor how they evaluate burns and differentiate between electrical and chemical burns, for the purpose of future adverse event assessments. The sponsor stated that they utilize the Draize score of 0-4, where a score of 4 represents burn. Electrical burns are clearly related to contact with the skin and clearly remote from the treatment site. Such burns may be due to the absence of gel applied under the electrodes. The sponsor stated that they had modified the portion of the electrode which was denuded, leading to the burns observed. Dr. Rappaport stated that such changes should be documented and submitted. Dr. Lee concurred that the sponsor should document such device changes, as he is concerned about the safety of the device.

Dr. McCormick asked about the pediatric pharmacokinetic study. Dr. Gross stated that the study is in six normal, healthy volunteers. Dr. McCormick stated that we want to see safety and pharmacokinetic data in pediatric patients younger than age 10. The sponsor should consult the NIH regulations on the protection of human subjects in studies, particularly the protection of pediatric subjects. The sponsor stated that parents will clearly have to provide informed consent. Dr. McCormick stated that labeling for only pediatric patients older than age 5 is not acceptable.

Summary/Sponsor's Questions:

We summarized the Agency's recommendations and the meeting discussion points, including a review of our answers to the sponsor's questions (Attachment 4):

Question 1. A summary of preclinical studies that will be conducted on patches representing the commercial image is provided. Does FDA agree that the plan is sufficient for NDA filing and meets NDA requirements to support the Package Insert claims for the intended use of the Northstar System.

Discussion: The sponsor should submit their pharmacology/toxicology protocols (sensitization, irritation studies) as soon as possible, prior to study initiation. These should include specification of the current, voltage, and formulation applied.

Clinical Question: Does FDA agree that we will proceed to Phase 3 clinical study of the Northstar System?

Response: Yes, the Agency agrees.

Clinical Question 1: Does FDA agree that the Phase 3 clinical program and protocol designs are adequate to support the intended Package Insert claim and allow the NDA to be filed?

Clinical Question 2: Are there comments/suggestions/additional requirements with respect to controls, blinding, clinical endpoints, use/choice of VAS, statistical analysis, number of patients, entry criteria, and other?

Clinical Question 3: Are the total number of subjects entered into previous clinical and to be entered into Phase 3 clinical studies sufficient to support the indication?

Discussion: The Agency made several recommendations to the sponsor:

1. The sponsor should study _____ and geriatric patients as part of their Phase 3 clinical program.
2. The sponsor should analyze for burns in their Phase 3 studies and capture data on adhesiveness and burns in the case report forms.
3. The sponsor should not limit their studies to cannulation. The sponsor should expand their Phase 3 plan to include other intended uses.
4. The sponsor should study at least 1000 subjects/patients in their Phase 3 program to allow for an adequate safety database. The sponsor should ensure that a diverse patient population is captured. The use of MIPs should be rationalized.
5. Patients should have in-person follow-up visits at 24 hours (and beyond, if necessary).
6. The sponsor must consider their proposed labeling _____
7. The sponsor must study _____ the systemic effects of applications to multiple sites in a short period of time.

Clinical Question 4: FDA has suggested that lidocaine pediatric plasma levels should be determined. Does FDA agree that this will be accomplished by supplementing existing pharmacokinetic information with a six-subject pharmacokinetic study in normal 10-15 year old children?

Discussion: The sponsor should develop a pharmacokinetic proposal. Three options were proposed: 1) a six-subject study, 2) obtaining single blood samples from patients enrolled in the Phase 3 studies, or 3) utilization of the _____ technique. This latter option requires further intra-Agency discussion.

We reaffirmed that an in vivo bioequivalence study will not be required to establish comparability between the pilot and commercial products, since no changes in formulation or manufacturing process are anticipated. Requirements beyond this should be discussed later.

CMC requirements include submission of results of:

1. Appearance test
2. Identity test (active ingredient)
3. Functionality test for adhesiveness (finished product)
4. Total degradation products

Dr. Rappaport inquired about the sponsor's plans for electronic submissions. Dr. Gross asked if it would be too late to discuss that at the pre-NDA meeting. He stated that the case report forms are not done electronically, although they are developing that capacity. Dr. Rappaport stated that postponing the discussion until the pre-NDA meeting would be too late, and Dr. McCormick encouraged the sponsor to compile an electronic submission if they are able. Dr. Gross stated that they will address the issue, although it is a significant effort for a device company to undertake.

Dr. Jenkins reinforced that we want to see more pediatric pharmacokinetic data. The sponsor must address the contamination issue.

Dr. Rappaport informed the sponsor that Dr. Permutt has statistical comments regarding the experimental design of the proposed studies. Specifically, he does not feel that utilizing generalized estimating equations based on assumed gamma distributions of response variables is advisable. These points should be discussed in more detail at a later date, and we will review their proposed methods in protocols that the sponsor submits.

Dr. Rappaport adjourned the meeting.

Action Items: In addition to the items summarized above, the following action items are established:

1. We will issue a copy of the official meeting minutes to the sponsor.
2. We will check with the Office of General Counsel to determine what type of information is considered to be public domain.
3. We will provide the sponsor with clarification on which studies are required for submission of a 505(b)(1) application. We will evaluate the sponsor's requirements for the epinephrine component of the proposed system.
4. We will provide the sponsor with the regulations regarding labeling of the proposed device.
5. The sponsor will submit information regarding the differences between their proposed product and existing products.
6. The sponsor must obtain additional pharmacokinetic data from patients enrolled in their Phase 3 studies, to explain the increasing blood lidocaine concentrations observed in their two previous pharmacokinetic studies.
7. The sponsor will provide documentation of the differences between the MIP2 and MIP3 patches.
8. The sponsor will provide information from their available safety database.

Minutes prepared by: Debbie Fong, Pharm.D.

Minutes concurred by Chair: Bob Rappaport, M.D.



The image shows two handwritten signatures in black ink. The top signature is 'Debbie Fong' and the bottom signature is 'Bob Rappaport'. Each signature is written over a solid horizontal line.

20 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

CC: IND 48,365
HFD-170/Division Files
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HFD-102/J. Jenkins
HFD-170/ C. McCormick
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HFD-940/A. Hussain
HFZ-410/K. Lee

Drafted by: D. Fong 10/11/99

Revised: 10/13/99 per H. Blatt; 10/14/99 per A. Hussain, L. Jean, A. Goheer, R. Uppoor;
10/15/99 per M. Theodorakis, A. D'Sa, K. Lee, B. Rappaport, C.P. Moody

Initialed by: T. Permutt, S. Doddapaneni 10/13/99; S. Kim, S. Grosser, A. D'Sa 10/14/99;
C. McCormick 10/15/99

Final: *SPM / 10-15-99*
Filename: 48365 (BD) EOP2MM 091699.doc



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

IND 48, 365

Becton and Dickinson
One Becton Drive
MC-440
Franklin Lakes, New Jersey 07417

Attention: Aileen Gilbert
Regulatory Affairs

Dear Ms. Gilbert:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Iontophoresis lidocaine of drug delivery system containing a fixed combination of lidocaine and epinephrine.

We refer to the meeting between representatives of your firm and FDA on ~~January 13, 1999~~

A copy of our minutes of that meeting is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, please contact Ken Nolan, Consumer Safety Officer, at (301) 827-7410.

Sincerely,

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care
and Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

- **Discussion Points:**

- Introductory Remarks:**

- The Sponsor gave a brief presentation regarding the issues to be discussed during the meeting including the briefing package dated December 15, 1998.
 - In response to the Agency's request for information letter dated January 8, 1999, Becton Dickinson representatives (the sponsor) noted the comments were helpful and many would be ultimately addressed in the NDA. Since time was limited, the sponsor wished to keep the discussion focused on the five questions.
 - The sponsor reviewed the status of clinical development plans for the completion of Phase II and III clinical studies including:
 - 500 volunteers had been tested in four Phase 1 protocols conducted under the IND
 - Subjects received multiple exposures in these studies; the sponsor currently has safety data on 1000-2000 exposures.
 - Recent pharmacokinetic study indicated that the small amounts of lidocaine delivered, producing local anesthetic effects, did not produce detectable systemic blood levels
 - The sponsor stated that they intend to provide the details of Phase III studies during an End-of-Phase II meeting which would be requested in the near future.

The following summarizes the discussions and agreements reached regarding the five questions submitted in the December 15, 1998 submission.

Question 1

Does the FDA agree that stability data on patches from the Phase III clinical supplies and stability sample manufacturing process will serve as the primary NDA stability data when supplemented with stability data on patches manufactured by the post-Phase III commercial manufacturing process?

Question 1 Discussion and Agreements

- The Agency agreed in principle regarding the Sponsor's proposal.
- The expiration dating period will be based on stability data from patches manufactured from pilot lots. These data will be supplemented with data on patches produced from commercial lots.
- It was agreed that the sponsor will provide initially in the NDA submission —
 - stability data from pilot lots of the drug product stored at the recommended conditions for the drug product as well as —
 - accelerated stability data. Additionally, the sponsor will provide — , stability data on patches from commercial lots stored at the recommended storage conditions and at 40°C.
- The sponsor agreed to provide additional stability data in an NDA amendment after the NDA is filed. These data will include the — data for patches from pilot lots stored under the conditions recommended in the labeling and the month data for patches from commercial lots. In addition, — , accelerated stability data for patches from commercial lots should be included in the amendment.
- The participants agreed that appropriate commitments to complete the stability program would be included in the initial NDA submission. Depending on the data trend an initial expiration dating period of two-years may be granted.

Question 2

Does the FDA agree that these patches are comparable to patches manufactured by the post-Phase III commercial manufacturing process? What additional information, if any, will be required to demonstrate comparability of patches manufactured by the Phase III clinical supplies and stability sample manufacturing process with the post-Phase III commercial manufacturing process?

Question 2 Discussion and Agreements

- The Agency indicated that based on the information presented at the meeting, patches produced by the pilot and commercial processes might be comparable. However, the Agency reserves the right to make a firm decision on this matter after it has had have the chance to review the data in the NDA submission.
- A minimum of — real time stability data should be included in the initial NDA filing. All the clinical and pharmacokinetic data will be generated using the pilot lots. The Sponsor will have to demonstrate that the manufacturing process for the pilot lots is comparable to that for commercial lots, and that the commercial lots are bioequivalent to pilot scale lots.

- Since all clinical data will be generated using the pilot lots, the Agency requested that the sponsor submit all available data on comparing pilot and commercial lots at the time of NDA submission.
- The sponsor was also asked to submit any data from animal experiments to determine the amount of drug penetrating into the skin (i.e., this will help confirm experimentally the theoretical calculations for the amount absorbed).
- The Agency noted while it may be reasonable not to use an in vitro release test, additional indirect tests for adequate quality control may be needed including conductivity test, pH, _____, etc.
- In lieu of an in vitro release test, the Sponsor needs to provide documentation that their proposed tests will assure the inter/intra batch reproducibility of the drug product.
- The sponsor confirmed that Phase III clinical studies will be conducted with patches manufactured by the pilot process, and this data will serve as primary safety and effectiveness data.
- The Center for Devices and Radiological Health requested the following data regarding the device:
 - Stability test confirming no leakage between hydrogel and electrical connector of electrode
 - pH change
 - Leachable materials
 - Conductivity test at different time points (i.e., _____)
 - Preclinical skin irritation data
 - AEs (i.e., skin burns noted at low pH levels)
 - Intended use of device
 - Working mode (including allowable tolerance of microprocessor and its safety)
- The sponsor agreed to submit the above information regarding the device prior to the EOPH meeting.
- The participants agreed that the criteria for filing 510K application would be discussed at the pre-NDA meeting.

Question 3

[Final product release and NDA stability will be based on the specifications and tests described in Attachment III-E of the January 13, 1999 Information Package].
Are these specifications and tests adequate?

Question 3 Discussion and Agreements:

- The participants agreed that assay of epinephrine degradation products, electrical conductivity _____ will be added to the regulatory release specifications and testing procedures. Another meeting to refine and clarify the specific release test criteria will be held at the sponsor's request.
- The sponsor proposed that it was not necessary to add a drug release test and that measurement of only _____ epinephrine degradation products was adequate.
- The Agency agreed that the Sponsor's rationale for not using an in vitro release test as a quality control test for this product appears to be reasonable because this is a highly soluble formulation.
- The Agency inquired whether in vitro tests with _____ had been conducted. The sponsor confirmed data were available and stated that the _____ and the method is not suitable for a quality control test.
- The Agency requested that the sponsor submit these data in their NDA and explain the reasons for not using an in vitro release test routinely.

Question 4

Does the FDA agree with this approach?

Question 4 Discussion and Agreements:

- The Agency agreed that a _____
- The Office of New Drug Chemistry will determine whether an additional _____ is acceptable for _____

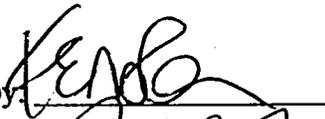
Question 5

We also wish to discuss FDA's receptivity to the possibility of our filing an NDA Amendment describing the post-Phase III commercial production process should we claim the Phase III clinical supplies production process in our initial NDA filing. We also wish to discuss the alternative of filing this as an NDA Supplement. Along these lines, we would also be seeking advice on the scheduling and timing of pre-approval inspections related to the filing of the initial NDA, an NDA Amendment or an NDA Supplement.

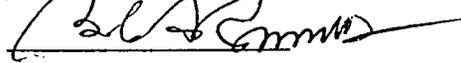
Question 5 Discussion and Agreements:

- The Agency proposed that an amendment may be submitted containing the commercial process data if these data were not filed in the original application. The data would need to be submitted no more than 2 months after the initial NDA submission in order for the data to be reviewed within the 10 month review cycle. Otherwise, these data should be handled through a post-approval Supplement.
- The Agency informed the sponsor that its goal is to respond to NDA applications within 10 months of the initial submission.
- The sponsor should be prepared for a pre-approval inspection at the time of the initial NDA submission.

Minutes Prepared by:



Chair's Concurrence:

**Attachments/Handouts:**

Attachment 1: List of Attendees

Attachment 2: List of Samples Distributed at Meeting

Attachment 3: Copies of Overheads Presented at Meeting

ATTACHMENT 1: LIST OF ATTENDEES

G. Baskinger – BDTS, Quality Management
H. Blatt – CDER, Clinical Reviewer
P. Green – BDTS, Research
M. Gross – BDTS, Regulatory Affairs
U. Jain – BDTS, Pharmaceuticals
T. Kosinski – BDTS, Business Director
K. Lee – CDRH, Medical Officer
C. Moody – CDER, Chief, Project Management Staff
K. Nolan – CDER, Project Manager
B. Rappaport – CDER, Deputy Division Director
V. Reddy – BDTS, Product Development
C. Skwara – BDTS, Manufacturing
S. Smith – BDTS, Project Manager
M. Theodorakis – CDER, Review Chemist
R. Uppoor – CDER, Clin., Pharm. And Biopharm. Team Leader

ATTACHMENT 2: LIST OF SAMPLES DISTRIBUTED AT MEETING

ATTACHMENT 3: COPIES OF OVERHEADS PRESENTED AT MEETING (NOT SUBMITTED PREVIOUSLY)

ATTACHMENT 1

LIST OF ATTENDEES

G. Baskinger	BDTS, Quality Management
H. Blatt	CDER, Clinical Reviewer
P. Green	BDTS, Research
M. Gross	BDTS, Regulatory Affairs
U. Jain	BDTS, Pharmaceuticals
T. Kosinski	BDTS, Business Director
K. Lee	CDRH, Medical Officer
C. Moody	CDER, Chief, Project Management Staff
K. Nolan	CDER, Project Manager
B. Rappaport	CDER, Deputy Division Director
V. Reddy	BDTS, Product Development
C. Skwara	BDTS, Manufacturing
S. Smith	BDTS, Project Manager
M. Theodorakis	CDER, Review Chemist
R. Uppoor	CDER, Clin., Pharm. And Biopharm. Team Leader

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6 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling