CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-486

CHEMISTRY REVIEW(S)

Team Leader Memo to file: NDA 21486
Ravi S. Harapanhalli, Ph.D.
HFD-170
October 1, 2004

Overall recommendation from CMC:

NDA is approvable pending resolution of outstanding deficiencies on the revisions to the specifications for the drug substances and the drug product, listed at the end of this memo.

The CMC section of the NDA was reviewed by Jila Boal, Ph.D. Her review was signed off into the DFS on September 30, 2004.

Description of the drug product and the iontophoretic device:

Lidopel™ is indicated for [redacted] . Lidopel™ (lidocaine HCl 2% and epinephrine 1:100,000 topical solution) is a sterile nonpyrogenic solution of lidocaine HCl and epinephrine in water. Lidopel™ is for iontophoretic dermal delivery using only the Dupel™ Iontophoresis system models for which the device labeling carries specific indications for Lidopel™ use. Each milliliter contains lidocaine HCl 20 mg/ml, epinephrine 10 mg/ml, sodium chloride 6 mg/ml, and sodium bisulfite 0.55 mg/ml. It may contain sodium hydroxide and/or hydrochloric acid for adjusting the pH to 3.8 to 5.5. The product is supplied in 1.8 ml cartridges.
(Note: The ODS/DMETS did not approve the trade name Lidopel™. Empi has agreed to propose an alternative name for Agency's consideration.)

The Iontophoresis System (K903093):

The Dupel™ Iontophoresis system consists of a dual channel microprocessor-controlled battery-powered DC current generator and electrodes. Dupel™ Iontophoretic System was cleared for marketing in 1990 with a 510(k) premarket notification process (K903093) as a substantially equivalent Class III device.

The Iontophoresis Electrodes (K912015, K970491, and K983484):

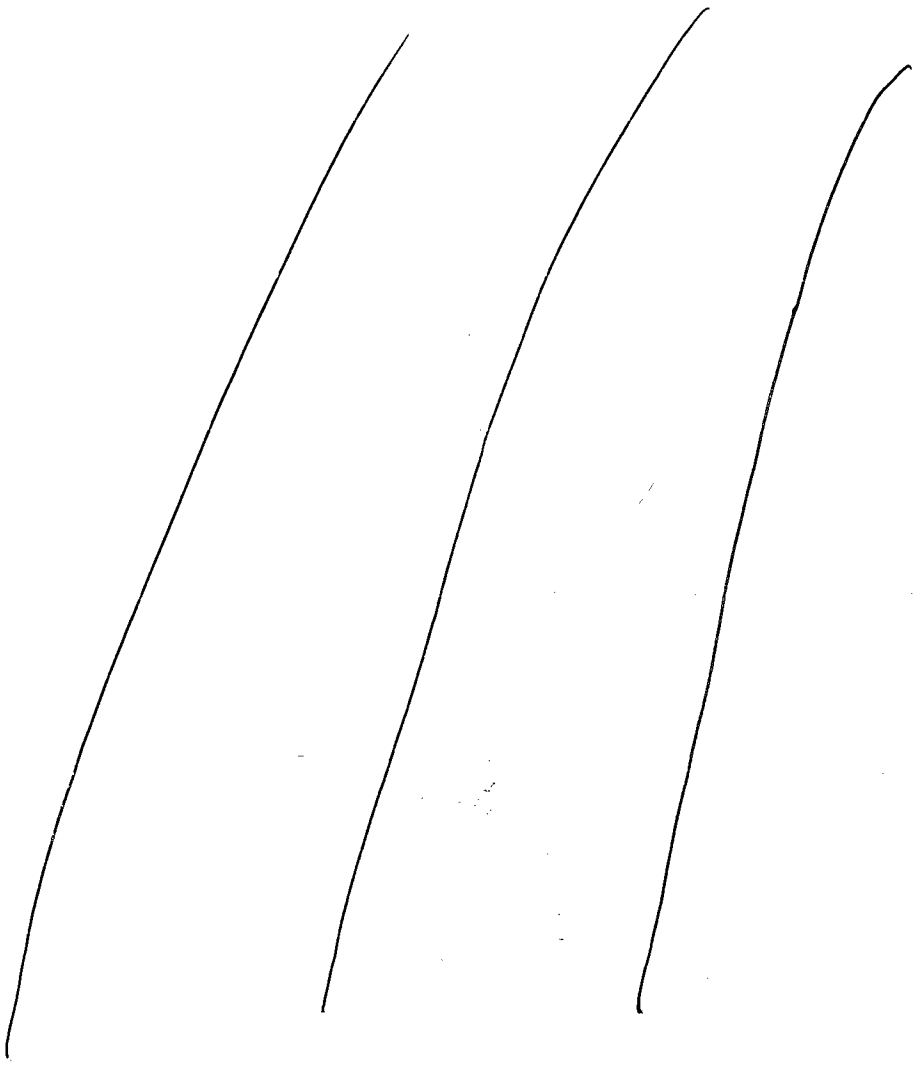
The Empi Dupel™ Iontophoresis drug delivery electrodes are composed of a pH buffering layer and absorbent drug reservoir that is hydrated before use. The Dupel™ Iontophoresis electrode is filled with the appropriate amount of Lidopel™ as indicated in the instructions for use supplied with the electrodes. Dupel™ electrodes consist of a drug delivery electrode, a self-adhering return electrode, and a cleaning wipe. Dupel™ Iontophoresis electrodes used with the Dupel™ Iontophoresis system have also been

cleared for marketing with a 510(k) premarket notification (K912015, K970491, and K983484).

The Dupel™ Iontophoresis Controller and Dupel™ Iontophoresis electrodes are manufactured by Empi at the following address:

Empi, Inc.
Clear Lake Industrial Park, Clear Lake, South Dakota 57226.

Labeling and Nomenclature:



Status of the DMFs and 510(k)s:

All the referenced DMFs are adequate to support this NDA. The referenced 510(k)s for the controller (K903093) and the electrodes (K912015, K970491, and K983484) are current and are on file in the CDRH. Earlier, the 510(k)s were cleared by CDRH with a caveat that Empi may neither label not promote their devices for use with specific drugs, nor package drugs with their devices prior to FDA having approved the drugs for iontophoretic administration. This was based on CDRH position that the Agency's substantially equivalent decision did not apply to the drugs that the applicant would intend to label or promote for use with the devices. Therefore, the 510(k)s were resubmitted as part of this NDA. From our review point the product was considered a combination product of the drug and device, and in discussion with the Office of Combination Products, a consult was requested of the devices with CDRH and the 510(k)s were reviewed from CDER perspective.

CDRH Consult request dated November 24, 2003:

The following sections described in Volume 1.7 of the NDA were consulted to CDRH with specific request to review the design controls, electrical and electrochemical specifications of the Dupel™ Iontophoresis Controller and the Dupel Iontophoresis Electrodes related to the iontophoretic delivery of Lidopel™. The CDRH consult review by Dr. Kevin Lee indicated that there were no concerns or issues with the devices if used in conjunction with the drug.

CMC Information request letter dated August 24, 2004:

Several questions concerning the specifications for the drug substances and the drug products, and the device components and specifications were communicated to Empi. The questions on the controller and electrodes were specifically related to the compatibility with the drug and some required updates to the 510(k)s. Empi's amendment dated September 10, 2004 addressed the device related comments and deficiencies but failed to address the two questions on the revisions to the specifications for the drug substances and the drug product. The outstanding deficiencies and the comments on labeling are listed below. These should be included in the action letter to Empi.

Outstanding CMC Deficiencies and Comments:

The specifications for the drug substances and the drug product need to be revised to conform to the ICH Q3A/B guidelines for the new drug applications as recommended below.

1. Provide the following revised specifications for lidocaine hydrochloride.
   a) Individual drug-related unspecified impurity or degradation product: NMT
   b) Total impurity: NMT
   c) . NMT

2. Provide the following revised specifications for epinephrine.

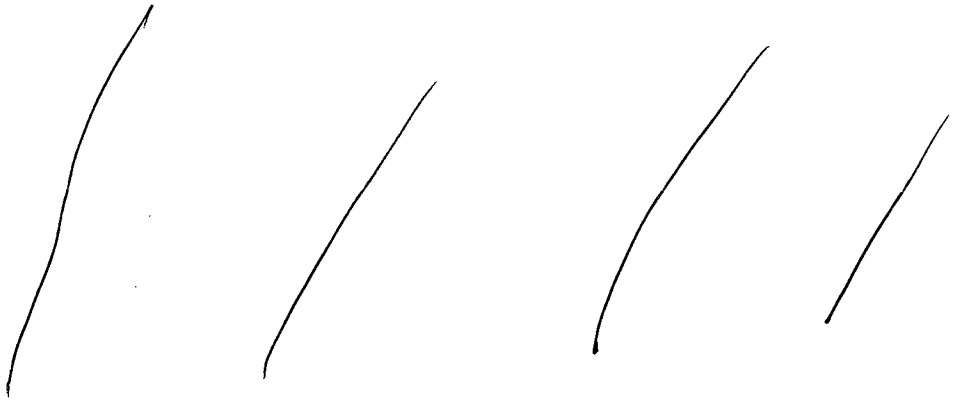
   a) NMT
   b) NMT
   c) Individual drug-related unspecified impurity: NMT
   d) Total known: NMT
   e) Total unknown: NMT

   (You may contact Septodont, Inc and request updated specifications listed in the DMFs hese DMFs are supported and cross referenced in the ANDA 84-048 that is referenced in your NDA.)

3. Revise the specifications for the degradation products of lidocaine and epinephrine in the drug product as follows.
   a. Individual unspecified and unidentified degradation products of lidocaine: NMT or whichever is lower.
   b. Individual unspecified and unidentified degradation products of epinephrine: NMT or whichever is lower.

4. Provide a statement of commitment that any changes in the Lidopel™ formulation manufacturing process and specifications by Novocol, and/or any changes to the Dupel Controller and electrodes would be appropriately filed in the Empi's NDA and the 510(k)s.

The following comments refer to the labels and labeling.



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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/

Ravi Harapanhalli
10/1/04 02:28:55 PM
CHEMIST

NDA 21-486

Tradename (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoresis) [For use with Empi Dupel® Iontophoretic Bi-Layer Ultra Electrodes and Dupel Iontophoretic Controller]

Empi, Inc.
599 Cardigan Road
St. Paul, MN 55126-4099

Jila H. Boal, Ph. D.

Division of Anesthetics, Critical Care, and Addiction Drug Products
(HFD-170)

Table of Contents

Chemistry Review Data Sheet

1. **NDA** 21-486

2. **REVIEW #:** 2

3. **REVIEW DATE:** 20-October-2004

4. **REVIEWER:** Jila H. Boal, Ph. D.

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Original	8-FEB-2002
Amendment (BC)	13-MAR-2002
Amendment (AR)	15-OCT-2002
Amendment (BZ)	29-JUL-2003
Amendment (BZ)	03-FEB-2004
Amendment (AZ)	7-JUN-2004
Amendment (BL)	11-JUN-2004
Amendment (BC)	10-September-2004
Amendment (BL)	17-September-2004

6. **SUBMISSION(S) BEING REVIEWED:**

Submission Reviewed	Submission Date
Amendment (BC)	19-October-2004

7. **NAME & ADDRESS OF APPLICANT:**

Name: Empi, Inc.
Address: 599 Cardigan Road
St. Paul, MN 55126-4099

Representative: Gary L. Yingling
Kirkpatrick & Lockhart LLP
1800 Massachusetts Ave., NW, Wash. D.C 20036
Telephone: (202) 778-9124

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: Pending
b) Non-Proprietary Name (USAN): Lidocaine HCl and Epinephrine
c) Code Name / # (ONDC only): not applicable
d) Chem. Type / Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 b (2), NDA # 20-530 (Iontocaine)
K863166, Iomed Phoresor II, model PM 700
K896703, Meditrode Electrodes

10. PHARMACOL. CATEGORY: Local Dermal Anesthesia

11. DOSAGE FORM: Solution for topical iontophoresis

12. STRENGTH/POTENCY: (20 mg/mL) lidocaine HCl and (10 µg/mL) epinephrine
/ — _ idocaine HCl and — epinephrine in 1.8 mL

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

_X_ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Lidocaine
Acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-;

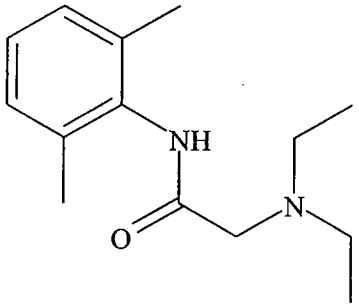
Or

2-(Diethylamino)-2',6'-acetoxylidide.

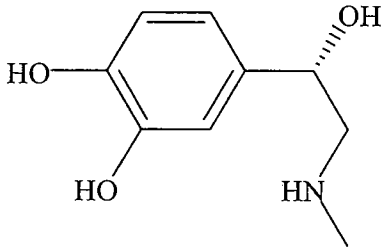
CAS-[137-58-6]

$C_{14}H_{22}N_2O.HCl.H_2O$

MW 288.81

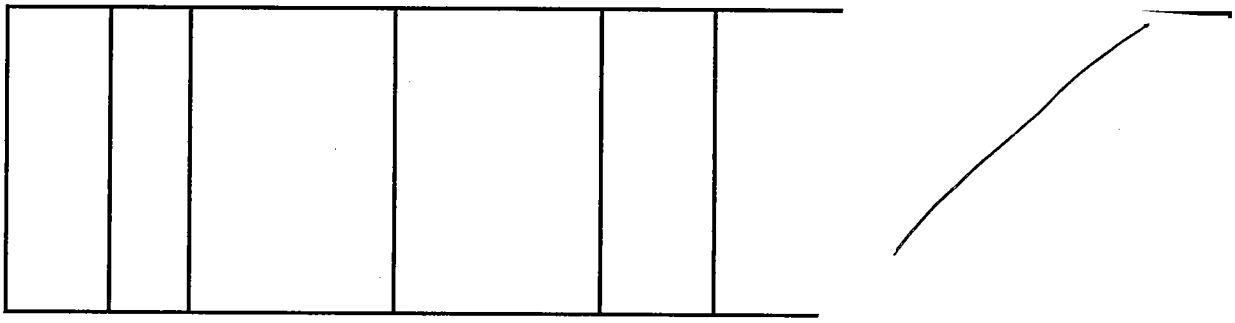


Epinephrine
(-)-3, 4-Dihydroxy-α-[(methylamino) methyl] benzyl alcohol
CAS-[51-43-4]
$C_9H_{13}NO_3$
MW 183.20



17. RELATED / SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	10-Feb-2004	By P. Maturu, Ph. D.
	II			3	Adequate	30-Apr-2004	By Danae Christadoulou, Ph. D.
				4, and 7	Adequate		



[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since the last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	54,731	2% Lidocaine HCl and Epinephrine 1:100,000 via the Dupel® Iontophoresis System
ANDA Septodont, Inc.	84-048	Octocaine®(Lidocaine HCI 2% and Epinephrine 1:100,000, Injection, USP)
Iomed NDA	20-530	Iomed Iontocaine® and the Iomed Phoresor®
Empi 510 (K)s	**K903093, K912015, K970491, K983484, K863166, K896703**	**K903093** for Dupel® Iontophoresis System / Device **K912015, K970491** and **K983484** for Empi Dupel® Buffered Iontophoresis Electrodes **K863166**, Iomed Phoresor II, model PM 700 **K896703**, Meditrode Electrodes

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Consulted	N/A	N/A
EES	Acceptable.	08-Jan-2004	S. Adams

Pharm/Tox	From a pharmacology/toxicology perspective, this NDA submitted by Empi, Inc.for Lidopel™ may be approved.	23-Sep-2004	Adam M. Wasserman, Ph.D.
Biopharm	N/A	N/A	N/A
LNC*	Under review	01-OCT-2004	Dr. Poochikian and Mille
Methods Validation	To be submitted to the FDA labs.		
ODS / DMETS	Lidopel was not acceptable in reference to sound alike and look alike with Lidopen and LidoSite.	03-Sep-2004	Carol Holquist, R.Ph.
EA	Not Applicable (Exclusion claimed)	N/A	N/A
Microbiology	Not Applicable	N/A	N/A
CDRH (electrodes, microprocessor and current generator)	Found the electrical and electrochemical parts of the system "Acceptable"	07-Apr-2004	Kevin Lee

*LNC recommended name:

The Chemistry Review for NDA 21-486

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from CMC stand point. **This decision is based on the satisfactory response from the applicant to the deficiencies that were listed in the CMC Review Number 1. Please see the review and evaluation of applicant's response to these deficiencies in this review.**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Iontophoresis can be used as an alternative to hypodermic injection.

This application supports and seeks approval of Empi's Tradename™ (Lidocaine HCl 2% and Epinephrine 1:100,000 solution for Topical Iontophoresis) [For use with Empi Dupel® Iontophoretic Bi-Layer Ultra Electrodes and Dupel Iontophoretic Controller] fo

Drug Product:

The product is a drug /device combination and consists of two separate parts that are packaged together:

(A).The drug product part: Empi's Tradename™ solution.

The product is a solution of 2% lidocaine HCl and 1:100,000 epinephrine.

(B). The medical device part: Empi Dupel Iontophoresis Drug Delivery System:

a) Dupel® Dual Channel Iontophoresis Controller, which consists of the following two parts:

- A device that generates a controlled, direct current stimulus.
- Lead wires that connect the dual channel iontophoresis controller and electrodes.
- This is covered under the 510(k).....

b) Empi Iontophoresis Buffered Electrode, Dupel® II Iontophoresis Electrode System and Dupel®B.L.U.E.™ Small Iontophoresis Electrode which consists of the following parts:

- A drug delivery electrode.
- A Self-Adhering return (dispersive) electrode.
- These are covered under the 510(k)s ...

Empi's Tradename™ solution:

Tradename™ is supplied to the tissue via Dupel® Iontophoresis Electrodes that are placed on the skin. The Tradename ™ solution is introduced to the delivery electrode with a disposable

syringe from the bottom layer of the patch through the wicking layer. The solution is dispensed prior to the administration in a quick and uniform manner. Direct current, generated by the battery-powered Dupel® device, is applied through the drug delivery and return electrodes.
Iontophoresis is a drug delivery method that uses an externally generated low level of electric current to deliver water-soluble, charged drugs into the skin.

, both drugs are delivered by the Dupel® Iontophoresis System from the positive electrode (drug delivery electrode) to provide dermal analgesia.

The Tradename ™ solution is an solution containing lidocaine HCl (20 mg/mL), epinephrine (10 µg/mL), sodium chloride (6 mg/mL), and sodium bisulfite (0.55 mg/mL) in water for injection. The quality of each excipient with respect to its electrochemical application exceeds the respective USP monograph requirements for that excipient and has been shown to be suitable for iontophoresis. The tradename ™ solution is thus adequate for electrochemical application. The tradename ™ formulation is simple and without unconventional excipients. The formulation contains minimum number of excipients and supports the criteria for iontophoretic application (i.e., there is minimal interference in electrical transport of lidocaine from extraneous ions in the dosage form due to the excipients).

Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action. Epinephrine increases the depth and duration of anesthesia, presumably because of its vasoconstrictor activity, which decreases the rate of removal of lidocaine from the site of administration.

The tradename ™solution is essentially the same as, except for the labeling, the drug product Octocaine® (2% Lidocaine HCl and Epinephrine 1:100,000) supplied to Empi by Septodont Inc. Octocaine® ANDA 84-048 is FDA approved for the production of local anesthesia by injection and nerve block. The ANDA for Octocaine® is held by Septodont, Inc., of New Castle, Delaware. Tradename™ will be manufactured, packaged and labeled at Novocol Pharmaceutical of Canada, Inc. Cambridge, Ontario N1R-6X3, CFN: 9615375. Detailed information on the synthetic process, starting material, manufacturing, in-process controls, analytical methods, specifications, purity, excipients, packaging and stability of the Tradename™ drug product were presented in the ANDA # 84-048. Current status of the ANDA indicated that there is no pending CMC issues in the ANDA 84-048 and that the latest Annual update was dated April 4, 2002.

Tradename ™ 1.8 mL solution is packaged in a cartridge — for single use and does not contain microbial preservative. The packaging design and closure system is identical to that of the approved Octocaine® product. Tradename ™ has a 20-months expiration dating period when stored in its commercial container closure system. The expiration dating was supported by the stability data in the ANDA 84-048 for Octocaine (approved Prior to Jan 1, 1982). The appropriateness of marketing the drug solution in cartridge form for iontophoretic application has been discussed with the medical discipline.

Empi performed an in vitro stability experiment to demonstrate the stability of Tradename ™ solution under iontophoretic condition. In-Vitro stability, study # 00-5-05.0, was performed by using the **K983484** electrode (size —, fill volume —. This size represents a typical worst case scenario since it has the highest current density being used. The study was able to show that the Tradename™ solution remains stable under the iontophoretic condition.

The buffering capacity of these electrodes when used with the Tradename ™ product were demonstrated (Study # 01-5-08.0). The results showed that the Empi Dupel® Iontophoresis Electrodes maintain the pH of the Tradename™ at — regardless of the initial pH as long as the drug product is within product specifications.

Outstanding deficiencies with respect to the Tradename ™ solution were as follows:

DMETS did not recommend the use of the proprietary name Lidopel. In reviewing the proprietary name, the primary concerns were related to look-alike and / or sound alike confusion with Lidopen and LidoSite. Empi has agreed with DMETS comment and has dropped the proprietary name Lidopel and has committed to work on a new name

With respect to the established name for this product, the HFD-170 division has decided on the use of the following established name —

With respect to the labeling of the solution product, the outstanding issues that were indicated in the CMC Review number 1 were satisfactory addressed by Empi and were reflected in the latest patient package insert label.

The Medical Device: Empi Dupel Iontophoresis Drug Delivery System:
The Dupel® Iontophoresis Controller and Dupel® Iontophoresis Electrodes were manufactured by Empi at the facility located at Clear Lake, South Dakota, CFN: 1721293. Empi iontophoresis drug delivery Controller was cleared for marketing on October 11, 1990 under the 510(k) Document Control number (D.C. number) K903093. —

The Dupel. Buffered Iontophoresis Electrode System consists of an active drug delivery electrode and a return electrode. These electrodes are designed for single patient, one application use. There are multiple sizes and shapes of drug delivery electrodes to accommodate placement at different body sites. The one size return electrode is usable with all drug delivery electrode sizes. Both electrodes have buffering capability to control the surface pH between 4-8 for up to a [redacted] mA.min treatment dose or session. The active electrode is without the medication. Prior to the start of treatment the appropriate amount of the Tradename™solution is introduced through a syringe to the delivery electrode according to the label instruction. Prior to treatment, the surface of the return electrode is slightly dampened (1-2 drops) with water for injection.

Since the original clearance date of October 11, 1990, minor modifications- not to be significant enough to warrant a new 510(k)- have been implemented to the battery driven component of this device. Thus, D.C. number **K903093** still holds for the battery driven part.

[redacted] These electrodes have gone through substantial modifications and were described in different 510(k)s. The final conclusion from CDRH was that the device is substantially equivalent to its predicates. The device plus electrodes were considered safe with respect to material of construction, mode of operation, and performance characteristics. The effectiveness of Tradename drug product to be used with the electrode and the device in this NDA is reviewed for its intended application by this reviewer.

In this review the focus was on describing the specifics of the electrodes used in pre-clinical, clinical and stability studies related to the NDA 21-486. The electrodes that were used in the in-vitro, in-vivo (animal), and the clinical studies of Empi Tradename™, their 510(k) clearance identification number, and their usage in various Empi studies are summarized in the original NDA submission (see Table 4-3 on page 11 CMC section 4, in volume 2 of 21). The NDA clinical studies made use of various sizes of **K970491** delivery electrodes and the unique size of 45.2 cm^2 of **K912015** return electrode.

The specifics of the to be marketed electrodes were described under the 510(k) D.C. number **K9834840.** The major difference between the **K970491** delivery electrodes and the **K9834840** electrodes was the change in the size of the electrode [redacted]

Outstanding deficiencies with respect to the device component were identified and were listed in the CMC Review # 1 and were conveyed to the applicant in the IR letter of August 24, 2004. The amendment of September 17, 2004 contained the response. The responses were found satisfactory and were documented in the CMC Review # 1.

Drug substance(s):
Empi's Tradename ™ product contains two drug substances and both are USP grade.
(1) Lidocaine HCl, USP and (2) Epinephrine,USP.

- Lidocaine HCl is manufactured by
- Epinephrine is manufactured by

DMFs supported and cross referenced in ANDA 84-048.
DMFs are adequate.

The DMFs have been recently updated to comply with the ICH Q 3A recommendations for the level of impurities and degradation products. In order to establish consistency in release specifications for the drug substances in the NDA and their corresponding DMFs, the specifications for the drug substances in the NDA should be updated according to the specifications in their respective DMFs.
Empi should update the specifications for the two drug substances according to the specifications listed in the DMFs

Lidocaine HCl has a retest period of at least
Epinephrine has a retest period of

B. Description of How the Drug Product is Intended to be Used:
For Iontophoretic administration, the Dupel® Dual Channel Iontophoresis System (Empi, Inc.) and Dupel B.L.U.E.™ (Bi-Layer Ultra Electrode) Iontophoresis Electrodes are used according to the instructions for use for the Dupel® Iontophoresis System and the Dupel B.L.U.E.™ (Bi-Layer Ultra Electrode) Iontophoresis Electrodes. The Instructions for Use are provided in the respective package inserts (i.e., the package insert for the electrodes, and the package insert for the battery driven component, the Dupel® Dual Channel Iontophoresis System).

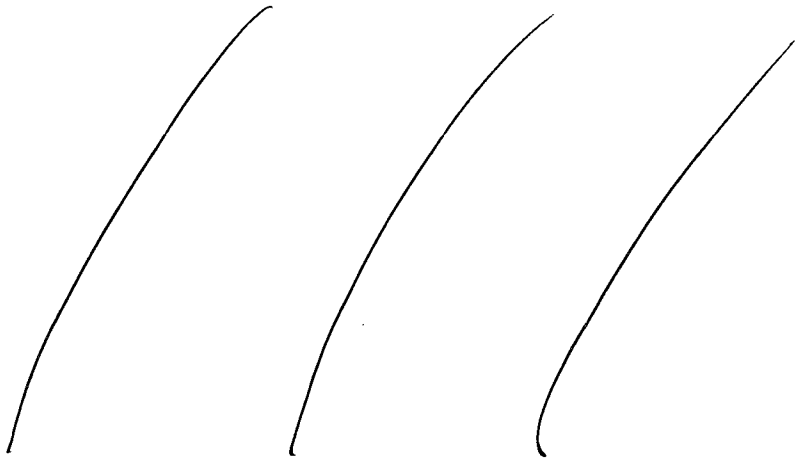
The Dupel® Dual Channel Iontophoresis System (Empi, Inc.) Instructions for use is a small booklet that is included in the Dupel® Dual Channel kit. The manual tells how to operate the DUPEL Iontophoresis Device. A copy of this manual is attached at the label section of the CMC Review # 1.

1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process



C. Basis for Approvability or Not-Approval Recommendation
Response to the deficiencies of the IR letter dated August 24, 2004 were satisfactory. These are reviewed in this CMC review number 2.

III. Administrative

A. Reviewer's Signature
Electronically Captured

B. Endorsement Block

Jila H. Boal, Ph. D, CMC Reviewer/ September 27, 2004
Ravi S. Harapanhalli, Ph. D, Chemistry Team Leader/
Lisa Malandro, Project Manager/

C. CC Block

7 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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/s/

Jila Boal
10/25/04 04:29:06 PM
CHEMIST

Ravi Harapanhalli
10/25/04 04:51:07 PM
CHEMIST
AP recommended. MVP for in vitro drug release testing should be initiated.

NDA 21-486

Empi (Lidocaine HCl and Epinephrine) 2%, 1:100,000 Topical Solution for Dermal Iontophoresis with the Empi Dupel® Topical Iontophoresis System

Empi, Inc.
599 Cardigan Road
St. Paul, MN 55126-4099

Jila H. Boal, Ph. D.

Division of Anesthetics, Critical Care, and Addiction Drug Products
(HFD-170)

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8. Drug Product Stability

III. INVESTIGATIONAL FORMULATIONS
IV. ENVIRONMENTAL ASSESSMENT
V. METHODS VALIDATION
VI. LABELING
VII. ESTABLISHMENT INSPECTION
VIII. REFERENCE PUBLICATIONS:
IX. DRAFT DEFICIENCY LETTER
X. REVIEW OF AMENDMENT NO.011, DATED SEPTEMBER 10, 2004
XI. LIST OF DEFICIENCIES TO BE COMMUNICATED

Chemistry Review Data Sheet

1. **NDA** 21-486

2. **REVIEW #:** 1

3. **REVIEW DATE:** 28-June-2004
   REVISED: 24- Sept-2004

4. **REVIEWER:** Jila H. Boal, Ph. D.

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
None	

6. **SUBMISSION(S) BEING REVIEWED:**

Submission Reviewed	Submission Date
Original	8-FEB-2002
Amendment (BC)	13-MAR-2002
Amendment (AR)	15-OCT-2002
Amendment (BZ)	29-JUL-2003
Amendment (BZ)	03-FEB-2004
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Amendment (BC)	10-September-2004
Amendment (BL)	17-September-2004

7. **NAME & ADDRESS OF APPLICANT:**

Name: Empi, Inc.
Address: 599 Cardigan Road
St. Paul, MN 55126-4099

Representative: Gary L. Yingling
Kirkpatrick & Lockhart LLP
1800 Massachusetts Ave., NW, Wash. D.C 20036
Telephone: (202) 778-9124

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lidopel™ (to be revised)
b) Non-Proprietary Name (USAN): Lidocaine HCl and Epinephrine
c) Code Name / # (ONDC only): not applicable
d) Chem. Type / Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 b (2), NDA # 20-530 (Iontocaine)
K863166, Iomed Phoresor II, model PM 700
K896703, Meditrode Electrodes

10. PHARMACOL. CATEGORY: Local Dermal Anesthesia

11. DOSAGE FORM: Patch (Topical iontophoresis patch)

12. STRENGTH/POTENCY: (20 mg/mL) lidocaine HCl and (10 µg/mL) epinephrine / , lidocaine HCl and epinephrine in 1.8 mL

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

_X_ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Lidocaine
Acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-;

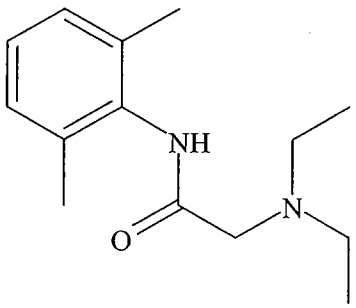
Or

2-(Diethylamino)-2',6'-acetoxylidide.

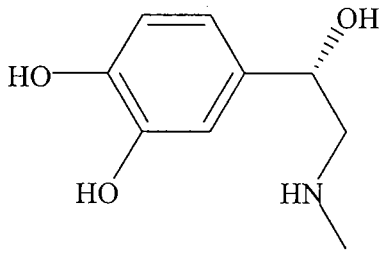
CAS-[137-58-6]

$C_{14}H_{22}N_2O.HCl.H_2O$

MW 288.81



Epinephrine
(-)-3, 4-Dihydroxy-α-[(methylamino) methyl] benzyl alcohol
CAS-[51-43-4]
$C_9H_{13}NO_3$
MW 183.20



17. RELATED / SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	3	Adequate	10-Feb-2004	By P. Maturu, Ph. D.
[redacted]	II	[redacted]	[redacted]	3	Adequate	30-Apr-2004	By Danae Christadoulou, Ph. D.

[redacted]				4, and 7	Adequate

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since the last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	54,731	2% Lidocaine HCl and Epinephrine 1:100,000 via the Dupel® Iontophoresis System
ANDA Septodont, Inc.	84-048	Octocaine®(Lidocaine HCI 2% and Epinephrine 1:100,000, Injection, USP)
Iomed NDA	20-530	Iomed Iontocaine® and the Iomed Phoresor®
Empi 510 (K)s	**K903093**, **K912015**, **K970491**, **K983484**, **K863166**, **K896703**	**K903093** for Dupel® Iontophoresis System / Device **K912015**, **K970491** and **K983484** for Empi Dupel® Buffered Iontophoresis Electrodes **K863166**, Iomed Phoresor II, model PM 700 **K896703**, Meditrode Electrodes

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Consulted	N/A	N/A
EES	Acceptable.	08-Jan-2004	S. Adams
Pharm/Tox	From a pharmacology/toxicology perspective, this NDA submitted by Empi, Inc.for Lidopel™ may be approved.	23-Sep-2004	Adam M. Wasserman, Ph.D.
Biopharm	N/A	N/A	N/A
LNC	Under review	Pending	Pending
Methods Validation	To be submitted to the FDA labs.	Pending	Pending
ODS / DMETS	Lidopel was not acceptable in reference to sound alike and look alike with Lidopen and LidoSite.	03-Sep-2004	Carol Holquist, R.Ph.
EA	Not Applicable (Exclusion claimed)	N/A	N/A
Microbiology	Not Applicable	N/A	N/A
CDRH (electrodes, microprocessor and current generator)	Found the electrical and electrochemical parts of the system "Acceptable"	07-Apr-2004	Kevin Lee

The Chemistry Review for NDA 21-486

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant's responses to the questions on the specifications for the drug substance and the drug product (Questions 1 and 2 in the IR letter sent on August 24, 2004) are pending. This NDA is approvable pending satisfactory response to deficiencies that are listed at the end of this review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Iontophoresis can be used as an alternative to hypodermic injection.
This application supports and seeks approval of Empi Lidopel™ (Lidocaine HCl and Epinephrine) 2%, 1:100,000 solution for dermal iontophoresis with the Empi Dupel® Iontophoresis controller and Empi Dupel® Iontophoresis Electrodes

Drug Product:

The product is a drug /device combination and consists of two separate parts that are packaged together:

(A).The drug product part: Empi's Lidopel™ solution.

Lidopel™ is a solution of 2% lidocaine HCl and 1:100,000 epinephrine.

(B). The medical Device part: Empi Dupel Iontophoresis Drug Delivery System:

a) Dupel® Dual Channel Iontophoresis Controller, which consists of the following two parts:

- A device that generates a controlled, direct current stimulus.
- Lead wires that connect the dual channel iontophoresis controller and electrodes.
- This is covered under the 510(k).....

b) Empi Iontophoresis Buffered Electrode, Dupel® II Iontophoresis Electrode System and Dupel®B.L.U.E.™ Small Iontophoresis Electrode which consists of the following parts:

- A drug delivery electrode.
- A Self-Adhering return (dispersive) electrode.
- These are covered under the 510(k)s ...

Empi's Lidopel™ solution:

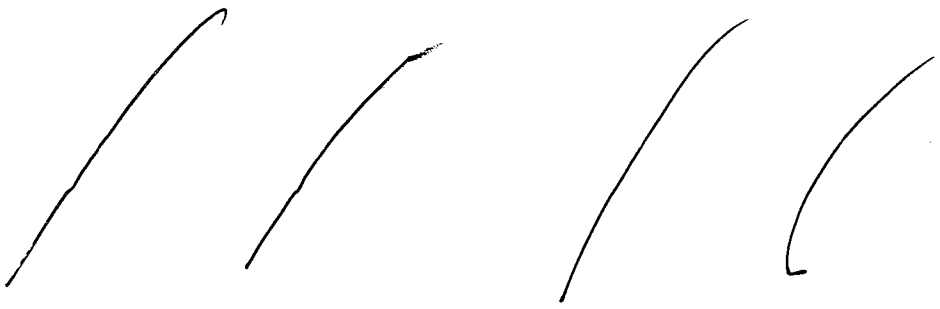
Lidopel™ is supplied to the tissue via Dupel® Iontophoresis Electrodes that are placed on the skin. The Lidopel™ solution is introduced to the delivery electrode with a disposable syringe

from the bottom layer of the patch through the wicking layer. The solution is dispensed prior to the administration in a quick and uniform manner. Direct current, generated by the battery-powered Dupel® device, is applied through the drug delivery and return electrodes. Iontophoresis is a drug delivery method that uses an externally generated low level of electric current to deliver water-soluble, charged drugs into the skin. both drugs are delivered by the Dupel® Iontophoresis System from the positive electrode (drug delivery electrode) to provide dermal analgesia.

Lidopel™ is an solution containing lidocaine HCl (20 mg/mL), epinephrine (10 µg/mL), sodium chloride (6 mg/mL), and sodium bisulfite (0.55 mg/mL) in water for injection. The quality of each excipient with respect to its electrochemical application exceeds the respective USP monograph requirements for that excipient and has been shown to be suitable for iontophoresis. Lidopel™ solution is thus adequate for electrochemical application. Lidopel™ formulation is simple and without unconventional excipients. The formulation contains minimum number of excipients and supports the criteria for iontophoretic application (i.e., there is minimal interference in electrical transport of lidocaine from extraneous ions in the dosage form due to the excipients).

Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action. Epinephrine increases the depth and duration of anesthesia, presumably because of its vasoconstrictor activity, which decreases the rate of removal of lidocaine from the site of administration.

Lidopel™ is essentially the same as, except for the labeling, the drug product Octocaine® (2% Lidocaine HCl and Epinephrine 1:100,000) supplied to Empi by Septodont Inc. Octocaine® ANDA 84-048 is FDA approved for the production of local anesthesia by injection and nerve block. The ANDA for Octocaine® is held by Septodont, Inc., of New Castle, Delaware. Lidopel™ will be manufactured, packaged and labeled at Novocol Pharmaceutical of Canada, Inc. Cambridge, Ontario N1R-6X3, CFN: 9615375.
Detailed information on the synthetic process, starting material, manufacturing, in-process controls, analytical methods, specifications, purity, excipients, packaging and stability of the Lidopel™ drug product were presented in the ANDA # 84-048. Current status of the ANDA indicated that there is no pending CMC issues in the ANDA 84-048 and that the latest Annual update was dated April 4, 2002.



Lidopel™ 1.8 mL solution is packaged in a cartridge for single use and does not contain microbial preservative. The packaging design and closure system is

identical to that of the approved Octocaine® product. Lidopel™ has a 20-months expiration dating period when stored in its commercial container closure system. The expiration dating was supported by the stability data in the ANDA 84-048 for Octocaine (approved Prior to Jan 1, 1982).

Empi performed an in vitro stability experiment to demonstrate the stability of Lidopel™ under iontophoretic condition. In-Vitro stability, study # 00-5-05.0, was performed by using the [redacted] **K983484** electrode (size [redacted], fill volume [redacted]). This size represents a typical worst case scenario since it has the highest current density being used.
The study was able to show that the lidopel™ solution remains stable under the iontophoretic condition.

The buffering capacity of these electrodes when used with Lidopel™ were demonstrated (Study # 01-5-08.0). The results showed that the Empi Dupel® Iontophoresis Electrodes maintain the pH of the Lidopel™ at [redacted] regardless of the initial pH as long as the drug product is within product specifications.

Outstanding deficiencies with respect to Lidopel™ solution were as follows:

1. DMETS did not recommend the use of the proprietary name Lidopel. In reviewing the proprietary name, the primary concerns were related to look-alike and / or sound alike confusion with Lidopen and LidoSite.

2. Specifications for the level of drug substance related impurities and degradation products in the Lidopel™ drug product should be revised in accordance with the ICHQ3B (R) recommendations.

a) Individual unspecified and unidentified degradation products of lidocaine: NMT [redacted], or [redacted] whichever is lower.

b) Individual unspecified and unidentified degradation products of epinephrine: [redacted] or [redacted] whichever is lower.

Empi has agreed with DMETS comment and has dropped the proprietary name Lidopel and has committed to work on a new name. Empi stated in the Amendment 011 dated September 10, 2004 that is working with the contact manufacturer (ANDA 84-048) in providing the updated specifications (i.e., the above item 2). The above item 3 should be conveyed to the applicant (see the Draft Deficiency Letter at the end of this review).

The Medical Device: Empi Dupel Iontophoresis Drug Delivery System:
The Dupel® Iontophoresis Controller and Dupel® Iontophoresis Electrodes were manufactured by Empi at the facility located at Clear Lake, South Dakota, CFN: 1721293.

Empi iontophoresis drug delivery Controller was cleared for marketing on October 11, 1990 under the 510(k) Document Control number (D.C. number) **K903093**.

Executive Summary Section

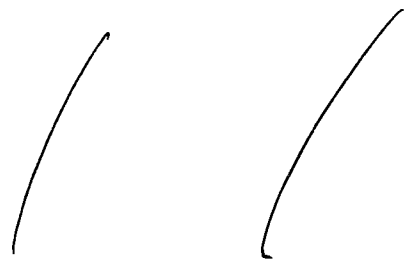
The Dupel® Buffered Iontophoresis Electrode System consists of an active drug delivery electrode and a return electrode. These electrodes are designed for single patient, one application use. There are multiple sizes and shapes of drug delivery electrodes to accommodate placement at different body sites. The one size return electrode is usable with all drug delivery electrode sizes. Both electrodes have buffering capability to control the surface pH between 4-8 for up to a [redacted] mA.min treatment dose or session. The active electrode is without the medication. Prior to the start of treatment the appropriate amount of Lidopel™solution is introduced through a syringe to the delivery electrode according to the label instruction. Prior to treatment, the surface of the return electrode is slightly dampened (1-2 drops) with water for injection.

Since the original clearance date of October 11, 1990, minor modifications- not to be significant enough to warrant a new 510(k)- have been implemented to the battery driven component of this device. Thus, D.C. number **K903093** still holds for the battery driven part.

These electrodes have gone through substantial modifications and were described in different 510(k)s. The final conclusion from CDRH was that the device is substantially equivalent to its predicates. The device plus electrodes were considered safe with respect to material of construction, mode of operation, and performance characteristics. The effectiveness of Lidopel™ drug to be used with the electrode and the device in this NDA is reviewed for its intended application by this reviewer.

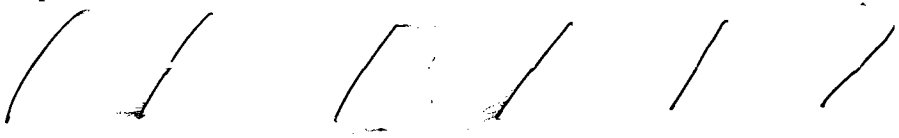
In this review the focus was on describing the specifics of the electrodes used in pre-clinical, clinical and stability studies related to the NDA 21-486. The electrodes that were used in the in-vitro, in-vivo (animal), and the clinical studies of Empi Lidopel™, their 510(k) clearance identification number, and their usage in various Empi studies are summarized in Tables 7 and 8. Table 7 can be found in the original NDA submission (see Table 4-3 on page 11, CMC section 4, in volume 2 of 21). The NDA clinical studies made use of various sizes of **K970491** delivery electrodes and the unique size of 45.2 cm^2 of **K912015** return electrode.

The specifics of the to be marketed electrodes were described under the 510(k) D.C. number **K9834840.** The major difference between the **K970491** delivery electrodes and the **K9834840** electrodes was the change in the size of the electrode [redacted]



Information such as chemical composition, specifications, and certificates of analysis of components of those parts of the electrode that are in direct contact with the patient skin and that are contributing to the electrophoretic performance of these electrodes were not described and were requested from the applicant. These were contained in the IR letter of August 24, 2004. These deficiencies are listed at the end of this review. The applicant's response was received on September 10, 2004 (Amendment No. 011). The responses were satisfactory (see review of the amendment in section **X** of the review).

Release specifications for the active electrodes were:



Release specifications for the return electrode were:

The packaged electrodes were put on stability

The outstanding issues identified for the device component are listed at the end of this review. These issues were conveyed to the applicant in the IR letter of August 24, 2004. The applicant's response to the deficiencies contained in the Amendment of September 10, 004 were reviewed and were found satisfactory (see section **X** of this review).

The outstanding issues with regard to the electrophoretic device are solely pertained to the label and packaging and are as follows:

Drug substance(s):
Empi Lidopel™ contains two drug substances and both are USP grade.
(1) Lidocaine HCl, USP and (2) Epinephrine,USP.

- Lidocaine HCl is manufactured by
- Epinephrine is manufactured by

DMFs were supported and cross referenced in ANDA 84-048.
DMFs are adequate.

The DMFs have been recently updated to comply with the ICH Q 3A recommendations for the level of impurities and degradation products. In order to establish consistency in release specifications for the drug substances in the NDA and their corresponding DMFs, the specifications for the drug substances in the NDA should be updated according to the specifications in their respective DMFs.
Empi should update the specifications for the two drug substances according to the specifications listed in the DMFs

The following deficiencies related to the control of the drug substance(s) level of impurities and degradation products were conveyed to the applicant in the IR letter of August 24, 2004.

1. Provide the following revised specifications for lidocaine hydrochloride:
a) Individual drug-related unspecified impurity or degradation product: NMT
b) Total impurity: NMT
c) . NMT

2. Provide the following revised specifications for epinephrine:
a) NMT
b) NMT

c) Individual drug-related unspecified impurity: NMT
d) Total known: NMT
e) Total unknown: NMT

Contact Septodont, Inc and request an updated specifications according to the specifications listed in the DMFs , as these DMFs are supported and cross referenced in the ANDA 84-048.

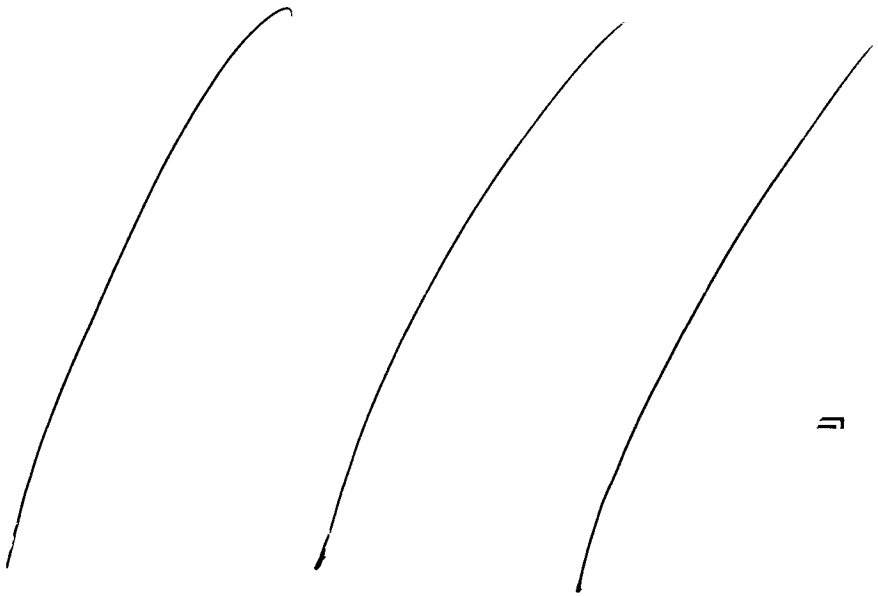
Lidocaine HCl has a retest period of at least
Epinephrine has a retest period of

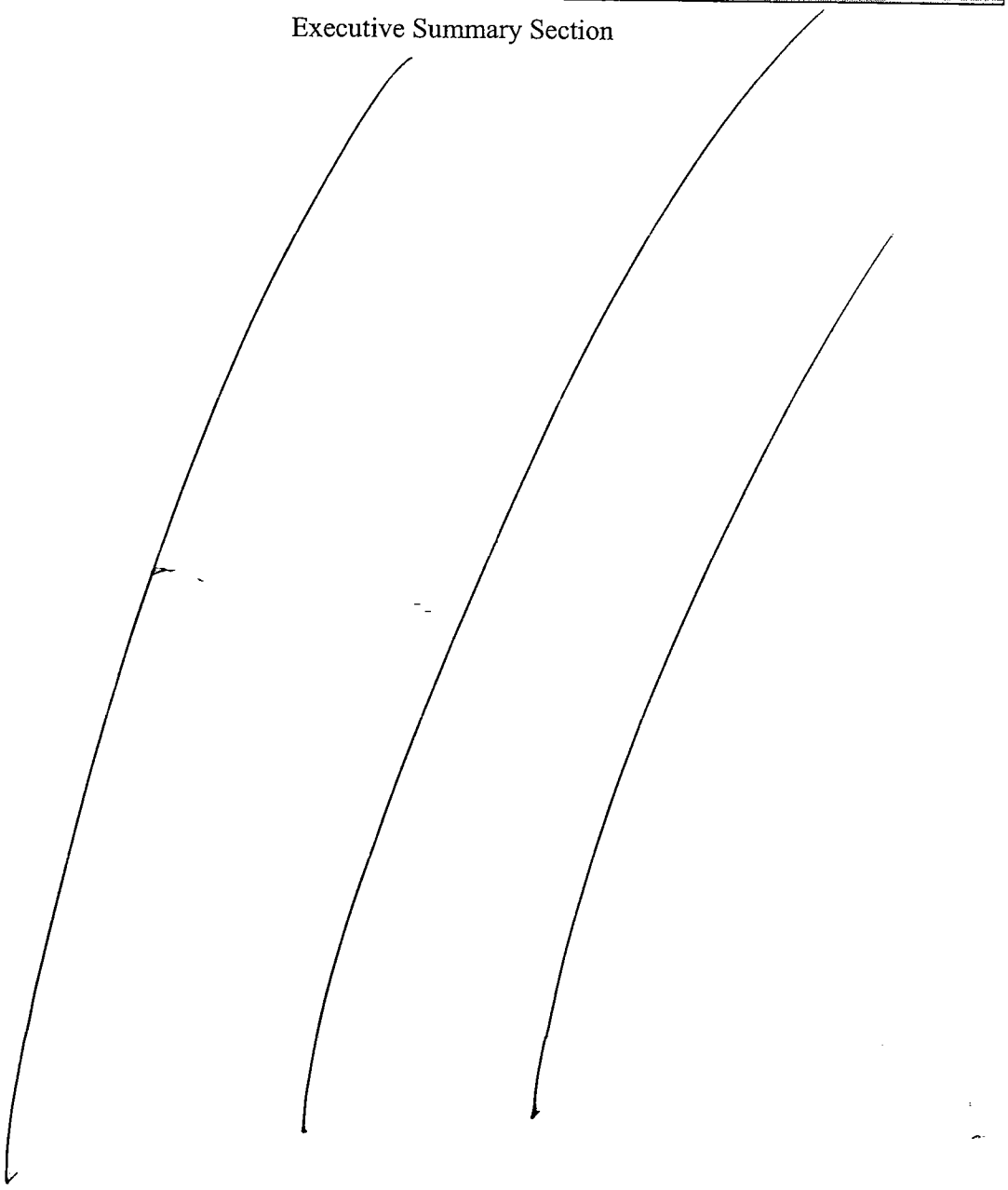
Empi stated in the Amendement 011 dated September 10, 2004 that it is working on responding to the above question and has contacted the DMF holders and that they would respond soon.

B. Description of How the Drug Product is Intended to be Used:

For Iontophoretic administration, the Dupel® Dual Channel Iontophoresis System (Empi, Inc.) and Dupel B.L.U.E.™ (Bi-Layer Ultra Electrode) Iontophoresis Electrodes are used according to the instructions for use for the Dupel® Iontophoresis System and the Dupel B.L.U.E.™ (Bi-Layer Ultra Electrode) Iontophoresis Electrodes. The Instructions for Use are provided in the respective package inserts (i.e., the package insert for the electrodes, and the package insert for the battery driven component, the Dupel® Dual Channel Iontophoresis System).

The Dupel® Dual Channel Iontophoresis System (Empi, Inc.) Instructions for use is a small booklet that is included in the Dupel® Dual Channel kit. The manual tells how to operate the DUPEL Iontophoresis Device. A copy of this manual is attached at the label section of this review.





C. Basis for Approvability or Not-Approval Recommendation

Deficiencies listed at the end of this review were conveyed to the applicant in the IR letter dated August 24, 2004. Partial response to these deficiencies were received in amendment 011 dated September 10, 2004 and the responses were found acceptable, except pending responses to two of the questions . Empi is working to provide response in a timely manor. The final decision with respect to approval of the CMC of this NDA is thus pending on submission of response to these two deficiencies. These deficiencies are basically the remaining two questions that were already conveyed to the applicant. In addition there are labeling comments that should be conveyed to the applicant and these are also listed at the end of this review.

III. Administrative

A. Reviewer's Signature

Electronically Captured

B. Endorsement Block

Jila H. Boal, Ph. D, CMC Reviewer/ September 27, 2004
Ravi S. Harapanhalli, Ph. D, Chemistry Team Leader/
Lisa Malandro, Project Manager/

C. CC Block

119 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Jila Boal
9/30/04 05:29:50 PM
CHEMIST
AE with comments

Ravi Harapanhalli
9/30/04 06:08:25 PM
CHEMIST
AE

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21486/000	Action Goal:	
Stamp:	11-FEB-2002	District Goal:	27-MAY-2004
Regulatory Due:	26-OCT-2004	Brand Name:	LIDOPEL(2% LIDOCAINE HCL
Applicant:	EMPI	Estab. Name:	AND EPINEPHRINE
	1800 MASSACHUSETTS AVE NOTHWEST	Generic Name:	LIDOCAINE HCL AND
	WASHINGTON, DC 20036		EPINEPHRINE 1:100,000
Priority:	4S	Dosage Form:	(TRANSDERMAL SYSTEM)
Org Code:	170	Strength:	2% LIDOCAINE/1:100000EP

Application Comment: THE DRUG PRODUCT IS LIDOCAINE HCL 2% AND EPINEPHRINE (1:100,000) TOPICAL SOLUTION FOR DERMAL IONTOPHORESIS WITH THE DUPEL IONTOPHORESIS SYSTEM. (on 12-APR-2002 by R. HARAPANHALLI (HFD-170) 301-827-7410)

FDA Contacts:	V. KAO	(HFD-170)	301-827-7410	, Project Manager
	R. HARAPANHALLI	(HFD-170)	301-827-7410	, Review Chemist
	ID = 108283			, Team Leader

Overall Recommendation: ACCEPTABLE on 08-JAN-2004by S. ADAMS (HFD-322)301-827-9051
ACCEPTABLE on 04-FEB-2003by S. ADAMS (HFD-322)301-827-9051
ACCEPTABLE on 23-OCT-2002by S. ADAMS (HFD-322)301-827-9051

Establishment: CFN FEI

No: AADA:

Responsibilities:

Profile: CSN OAI Status: NONE

Estab. Comment: THIS FACILITY (on 12-APR-2002 by R. HARAPANHALLI (HFD-170) 301-827-7410)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-APR-2002				HARAPANHALL
SUBMITTED TO DO	15-APR-2002	GMP			DAMBROGIOJ
DO RECOMMENDATION	16-APR-2002			ACCEPTABLE	DAMBROGIOJ
				BASED ON FILE REVIEW	
AC EI 3/00					
OC RECOMMENDATION	16-APR-2002			ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	07-NOV-2003				HARAPANHALL
OC RECOMMENDATION	10-NOV-2003			ACCEPTABLE	DAMBROGIOJ
				BASED ON PROFILE	

Establishment: CFN 1721293 FEI

EMPI INC

CLEAR LAKE INDUSTRIAL PARK HWY 22 EAST

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

CLEAR LAKE, SD 57226

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TDP OAI Status: NONE

Estab. Comment: NO CFN NUMBER IS ASSIGNED FOR THIS FACILITY, WHICH MANUFACTURES THE DUPEL IONTOPHORESIS SYSTEM AND DUPEL IONTOPHORESIS ELECTRODES NEEDED FOR THE TRANSDERMAL DELIVERY OF THE DRUG PRODUCT. THE 510(K) PREMARKET APPLICATION # K903093 WAS APPROVED BY CDRH ON OCTOBER 11, 1990. (on 12-APR-2002 by R. HARAPANHALLI (HFD-170) 301-827-7410)

lestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-APR-2002				HARAPANHALL
SUBMITTED TO DO	15-APR-2002	GMP			DAMBROGIOJ
DO RECOMMENDATION	25-APR-2002			ACCEPTABLE BASED ON FILE REVIEW	STHOMA

A CGMP INSPECTION WAS CONDUCTED AT THE ABOVE NAMED ESTABLISHMENT TO EVALUATE THE FIRM'S COMPLIANCE WITH MEDICAL DEVICE QUALITY SYSTEMS REGULATIONS REGARDING CONTROL, DESIGN, AND TESTING OF THE DUPEL IONTOPHORESIS SYSTEM AND DUPEL IONTOPHORESIS ELECTRODES. THE INSPECTION WAS CONDUCTED FROM 03/18-20/2002 AND COVERED THE "NEC" PROFILE CLASS FOR DEVICES. DRUG CGMPS WERE NOT COVERED SINCE THE ABOVE ESTABLISHMENT IS A DEVICE ESTABLISHMENT AND THE EES ASSIGNMENT WAS RECEIVED BY THE DISTRICT AFTER COMPLETION OF THE INSPECTION. NO FDA-483, INSPECTION OBSERVATIONS, WAS ISSUED DURING THIS INSPECTION.

SED ON THE INSPECTIONAL FINDINGS, I AM RECOMMENDING APPROVAL OF NDA 21486 FOR LIDOPEL (2% LIDOCAINE HCL AND EPINEPHRINE) AT THE DISTRICT LEVEL.

OC RECOMMENDATION	26-APR-2002	ACCEPTABLE	FERGUSONS

DISTRICT RECOMMENDATION

SUBMITTED TO OC	07-NOV-2003			HARAPANHALL
SUBMITTED TO DO	10-NOV-2003	GMP		DAMBROGIOJ
RECOMMENDATION	08-JAN-2004		ACCEPTABLE	STHOMA

BASED ON FILE REVIEW

A CGMP INSPECTION WAS CONDUCTED AT THE ESTABLISHMENT TO EVALUATE THE FIRM'S COMPLIANCE WITH MEDICAL DEVICE QUALITY SYSTEMS REGULATIONS REGARDING CONTROL, DESIGN, AND TESTING OF THE DUPEL IONTOPHORESIS SYSTEM AND DUPEL IONTOPHORESIS ELECTRODES. THE INSPECTION WAS CONDUCTED FROM 03/18-20/2002 AND COVERED THE MANUFACTURE OF THE DUPEL IONTOPHORESIS SYSTEM AND ELECTRODES. DRUG CGMPS WERE NOT COVERED AT THAT TIME SINCE THE ABOVE ESTABLISHMENT IS A DEVICE ESTABLISHMENT. NO FDA-483, INSPECTION OBSERVATIONS, WAS ISSUED DURING THIS INSPECTION.

BASED ON THE INSPECTIONAL FINDINGS, I AM RECOMMENDING APPROVAL OF NDA 21-486 FOR LIDOPEL (2% LIDOCAINE HCL AND EPINEPHRINE) AT THE DISTRICT LEVEL. THIS APPLICATION WAS PREVIOUSLY RECOMMENDED FOR APPROVAL AT THE DISTRICT LEVEL ON APRIL 24, 2002. IN ADDITION, SPECIFIC COVERAGE OF THIS APPLICATION IN REFERENCE TO DRUG CGMP'S HAS BEEN REQUESTED FOR COVERAGE DURING THE NEXT SCHEDULED INSPECTION (I.E. IN A MEMO TO FILE, DATED 12/24/2003).

OC RECOMMENDATION	08-JAN-2004	ACCEPTABLE	ADAMSS

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

DISTRICT RECOMMENDATION

Establishment: CFN 9615375 FEI 3002807757
NOVOCOL PHARMACEUTICAL CANADA INC
CAMBRIDGE, ONTARIO, CA

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: SVS OAI Status: NONE

Estab. Comment: THE FACILITY MANUFACTURES AND RELEASE TESTS THE DRUG PRODUCT SOLUTION OF 2% LIDOCAINE HCL ANDEPINEPHRINE (1:100,000). (on 12-APR-2002 by R. HARAPANHALLI (HFD-170) 301-827-7410)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-APR-2002				HARAPANHALL
SUBMITTED TO DO	15-APR-2002	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	16-APR-2002	GMP			DAMBROGIOJ
INSPECTION SCHEDULED	20-JUN-2002		19-JUL-2002		IRIVERA
INSPECTION PERFORMED	17-JUL-2002		17-JUL-2002		IRIVERA
DO RECOMMENDATION	23-OCT-2002			ACCEPTABLE ADEQUATE FIRM RESPONSE INSPECTION	ADAMSS
OC RECOMMENDATION	23-OCT-2002			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

SUBMITTED TO OC	07-NOV-2003			HARAPANHALL
SUBMITTED TO DO	10-NOV-2003	10D		DAMBROGIOJ
DO RECOMMENDATION	12-NOV-2003		ACCEPTABLE	DAMBROGIOJ
			BASED ON FILE REVIEW	
OC RECOMMENDATION	12-NOV-2003		ACCEPTABLE	DAMBROGIOJ
			DISTRICT RECOMMENDATION	

Establishment: CFN — FEI —

DMF No: AADA:

Responsibilities: —

Profile: CSN OAI Status: NONE

Estab. Comment: THIS FACILTIY — (on 12-APR-2002 by R. HARAPANHALLI (HFD-170) 301-827-7410)

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
INSPECTION PERFORMED	02-APR-2002		02-APR-2002		ADAMSS
SUBMITTED TO OC	12-APR-2002				HARAPANHALL
SUBMITTED TO DO	15-APR-2002	10D			DAMBROGIOJ
ASSIGNED INSPECTION T	16-APR-2002	GMP			DAMBROGIOJ
INSPECTION SCHEDULED	23-OCT-2002		02-APR-2002		ADAMSS
DO RECOMMENDATION	23-OCT-2002			ACCEPTABLE ADEQUATE FIRM RESPONSE INSPECTION	ADAMSS
OC RECOMMENDATION	23-OCT-2002			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
INSPECTION SCHEDULED	25-OCT-2002		30-DEC-2002		DAMBROGIOJ
SPECTION PERFORMED	27-NOV-2002		27-NOV-2002		DAMBROGIOJ

This inspection of an [redacted] was initiated in response to an assignment from HFD-130 and HFD-322 in relation to NDA 21486 for Lidocaine HCL/Epinephrine Transdermal System submitted by EMPI in Saint Paul, Minnesota. This inspection request was initiated under FACTS # 1186303. Based on the previous history of this firm, a GMP/pre-approval inspection was conducted under Compliance Programs 7356.002 & 7346.832 The profile class CSN was covered.

In accordance with the Compliance Program, the following systems were covered during this inspection: Quality, Laboratory, Materials and Equipment.

NOTE: [redacted]

DO RECOMMENDATION	04-FEB-2003		ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	04-FEB-2003		ACCEPTABLE	ADAMSS

DISTRICT RECOMMENDATION

SUBMITTED TO OC	07-NOV-2003		HARAPANHALL
OC RECOMMENDATION	10-NOV-2003	ACCEPTABLE	DAMBROGIOJ
		BASED ON PROFILE	

APPEARS THIS WAY
ON ORIGINAL

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