CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-486

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

13. PATENT INFORMATION

In the opinion and to the best knowledge of Empi, Inc., there are no patents that claim the drugs, the drug product, or the method of using the drug described in this Application ***[21 U.S.C. 355 (b) or (c) and 21 CFR 314.50(h)(2)].***

H. Philip Vierling
President & Chief Operating Officer
Empi, Inc.

14. PATENT CERTIFICATION

In the opinion and to the best knowledge of Empi, Inc., there are no patents that claim the drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drugs ***[21 CFR 314.50(i)(A)(ii)].***

H. Philip Vierling
President & Chief Operating Officer
Empi, Inc.

PEDIATRIC PAGE

NDA/BLA # : 21-486 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: September 26, 2003 **Action Date:** October 26, 2004

HFD-170 **Trade and generic names/dosage form:** TRADENAME (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System)

Applicant: Empi, Inc. **Therapeutic Class:** 4S

Indication(s) previously approved: none

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

Number of indications for this application: one

Indication #1: the iontophoretic production of local analgesia for superficial dermatological procedures such as venipuncture, shave removals and punch biopsies

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

- ☐ **Yes: Please proceed to Section A.**

X **No: Please check all that apply:** ____**Partial Waiver** __X__**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 (newborn) Tanner Stage_____
Max_____ kg_____ mo._____ yr. 17 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**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other: Two studies are deferred (1) safety and efficacy in patients ages 6 through 17 years, and (2) safety and efficacy in patients ages newborn through 5 years

Date studies are due (mm/dd/yy): (1) 10/31/08; (2) 10/31/11

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._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ 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:

{See appended electronic signature page}

Regulatory Project Manager

cc: **NDA 21-486**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Lisa Malandro
10/26/04 06:45:44 PM

NDA ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-486	-	
Drug: Empi Lidocaine HCl 2% and Epinephrine 1:100,000 Topical Solution		Applicant: Empi, Inc.
RPM: Lisa Malandro	HFD-170	Phone # 301-827-7416

Application Type: ( ) 505(b)(1) **(X)** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **(X)** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 20-530 Iontocaine ANDA 84-048 Octocaine

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	4S/6040400
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	October 26, 2004 July 26, 2004
❖ Special programs (indicate all that apply)	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	( ) Paid UF ID number
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation **(X)** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	

• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) 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 & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) (X) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	N/A
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(X) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes,**" a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	October 6, 2004

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	( ) 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)	October 26, 2004
• Most recent applicant-proposed labeling	September 17, 2004
• Original applicant-proposed labeling	October 15, 2002
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS – August 10, 2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	None
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	October 26, 2004
• Applicant proposed	September 17, 2004
• Reviews	DMETS – August 10, 2004
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Included
❖ Memoranda and Telecons	Included
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	July 30, 1999
• Pre-NDA meeting (indicate date)	July 20, 2001
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	B. Rappaport, MD 10/26/04 N. Chang, MD 10/1/04
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	A. Simone 10/5/04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	L. Kammerman, PhD 10/15/04
❖ Biopharmaceutical review(s) *(indicate date for each review)*	D. Lee, PhD 10/1/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	7/22/04
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	R. Harapanhalli, PhD 10/1/04 J. Boal, PhD 9/30/04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	N/A
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	A. Wasserman, PhD 9/23/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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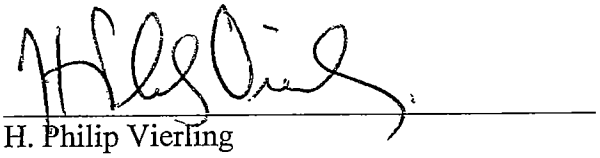
/s/

Lisa Malandro
10/27/04 12:16:13 PM

16. DEBARMENT CERTIFICATION

Empi, Inc. hereby certifies that it did not and will not use in any capacity, the services of any person debarred under §306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



H. Philip Vierling
President & Chief Operating Officer
Empi, Inc.

MEMORANDUM OF TELECONFERENCE

DATE: October 26, 2004

APPLICATION NUMBER: NDA 21-486, (Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoretic System)

BETWEEN:

Representatives of Empi, Inc.:

Kathleen Schmitt
Regulatory Affairs Manager, Empi

Ginny Conger
Quality Control Manager, Empi

[redacted]
Senior Staff Consultant

Rebecca Dandeker
Regulatory Counsel, Kirkpatrick & Lockhart

Gary L. Yingling
Regulatory Counsel, Kirkpatrick & Lockhart

AND

Representatives of HFD-170:

Bob Rappaport, MD, Director
Rigoberto Roca, MD, Deputy Director
Eric Duffy, Ph.D., Director, ONDCII
Nancy Chang, MD, Team Leader, Anesthetics
Thomas Permutt, Team Leader, Statistics
Arthur Simone, MD, Medical Officer
Robert Shibuya, M.D., Medical Officer
Jialyn Wang, DDMAC
Lisa Malandro, Regulatory Project Manager

SUBJECT: Labeling Agreements

A teleconference was held at 3:00 pm on October 26, 2004, in order for the Division to discuss their remaining labeling concerns with sponsor representatives. During the teleconference, agreement was made on all remaining issues and the Sponsor submitted revised labeling to reflect these changes via e-mail/fax. These communications have subsequently been processed to the NDA.

Lisa Malandro
Regulatory Project Manager

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/s/

Lisa Malandro
10/27/04 12:05:36 PM
CSO

Malandro, Lisa

From: Malandro, Lisa
Sent: Tuesday, October 26, 2004 5:03 PM
To: 'Dandeker, Rebecca L.'; Malandro, Lisa
Cc: Yingling, Gary L.; Higgins, Lorraine A.; 'kschmitt@empi.com'
Subject: RE: Empi, Inc., NDA 21-486
Importance: High

Gary,
As discussed following the teleconference, the Division is also requesting completion of two postmarketing commitments for pediatric studies. The details are as follows. If Empi agrees to these studies, then I will need a written confirmation (can be faxed or emailed as a PDF, but requires a signature) by 5:45 pm so that I can have the agreement processed to the NDA. Please contact me if I can be of assistance. Thanks, Lisa

1. Deferred pediatric study under PREA for the iontophoretic production of local analgesia for superficial dermatological procedures in pediatric patients ages six years through seventeen years.

Evaluate the safety and efficacy of Tradename when used on pediatric patients ages six through seventeen years across a variety of dermatological procedures. This study should include dose ranging in all age groups to discern differences from adult dosing requirements and to identify a dose which is safest and most efficacious for the procedures evaluated. If more than one delivery electrode patch could be required for a given procedure, dose ranging should be conducted for each electrode identified as appropriate for the condition treated.

Protocol Submission: by June 2005

Study Start: by December 2005

Final Report Submission: by October 2008

2. Deferred pediatric study under PREA for the iontophoretic production of local analgesia for superficial dermatological procedures in pediatric patients ages newborn through five years.

Evaluate the safety and efficacy of Tradename when used on pediatric patients ages newborn through five years across a variety of dermatological procedures. This study should include dose ranging in all age groups to discern any differences in dosing requirements compared to older pediatric patients and to identify a dose which is safest and most efficacious for the procedures evaluated. If more than one delivery electrode patch could be required for a given procedure, dose ranging should be conducted each electrode identified as appropriate for the condition treated.

Protocol Submission: by October 2007

Study Start: by April 2008

Final Report Submission: by October 2011

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/s/

Lisa Malandro
10/26/04 06:41:49 PM
CSO

Malandro, Lisa

From: Dandeker, Rebecca L. [rdandeker@kl.com]

Sent: Tuesday, October 26, 2004 12:30 PM

To: 'malandrol@cder.fda.gov'

Cc: Yingling, Gary L.; Higgins, Lorraine A.; 'kschmitt@empi.com'

Subject: Empi, Inc., NDA 21-486

Ms. Malandro,

Empi accepts and will implement the FDA's latest revision to the Empi package insert for Lidocaine HCl 2% and Epinephrine 1:100,000 Topical Solution, except for the following two points.

Attached is a document showing Empi's proposed changes, for discussion purposes at the 3:00 pm phone call scheduled between Empi and FDA. The attached document provides labeling for just the two package insert sections at issue, Indications and Usage and Dosage and Administration.

Gary L. Yingling
Rebecca L. Dandeker

Malandro, Lisa

From: Yingling, Gary L. [gyingling@kl.com]
Sent: Tuesday, October 26, 2004 7:26 PM
To: 'Malandro, Lisa'; Dandeker, Rebecca L.
Cc: Yingling, Gary L.; Higgins, Lorraine A.; 'kschmitt@empi.com'
Subject: RE: Empi Inc., NDA 21-486

Dear Ms Malandro

Empi accepts the labeling changes noted in this email.

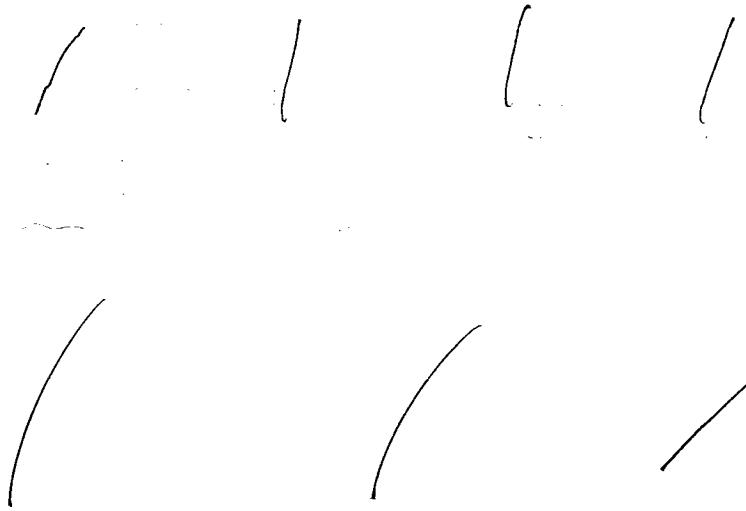
Gary L. Yingling
Counsel for Empi

-----Original Message-----
From: Malandro, Lisa [mailto:MalandroL@cder.fda.gov]
Sent: Tuesday, October 26, 2004 7:21 PM
To: 'Dandeker, Rebecca L.'; Malandro, Lisa
Cc: Yingling, Gary L.; Higgins, Lorraine A.; 'kschmitt@empi.com'
Subject: RE: Empi Inc., NDA 21-486

Thank you.

Dr. Rappaport has suggested revising #2 on page 11 to read as follows:

2.



Please send me an email agreeing to these changes :)

Thanks,

Lisa

-----Original Message-----
From: Dandeker, Rebecca L. [mailto:rdandeker@kl.com]
Sent: Tuesday, October 26, 2004 7:09 PM
To: 'malandrol@cder.fda.gov'
Cc: Yingling, Gary L.; Higgins, Lorraine A.; 'kschmitt@empi.com'
Subject: Empi Inc., NDA 21-486

Ms. Malandro,
As we discussed, please replace the previouslv-emailed carton labeling with the attached revised carton labeling. The revised carton labeling

Rebecca Dandeker
Gary Yingling

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/s/

Lisa Malandro
10/26/04 07:32:30 PM
CSO

Malandro, Lisa

From: Harper Velazquez, Tia M

Sent: Tuesday, October 19, 2004 9:25 AM

To: Malandro, Lisa

Cc: Mahmud, Alina; Beam, Sammie

Subject: NDA 21-486

Hi Lisa: I looked over the revised labeling, and it appears that the sponsor took our recommendations, and adjusted the labeling accordingly. To my understanding, the sponsor is using "Empi" as a place holder for the proprietary name. Once a proprietary name is submitted, please make sure and generate a consult so the name can be reviewed.

Thanks.

Tia M. Harper-Velazquez, Pharm.D.
LT, USPHS
Safety Evaluator
Office of Drug Safety, Division of Medication Errors & Technical Support, HFD-420
Phone: (301) 827-0925
Fax: (301) 443-9664

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/s/

Lisa Malandro
10/26/04 06:47:18 PM
CSO

Teleconference Date: September 1, 2004
DRUG: Lidopel
NDA: 21-486

INDUSTRY PARTICIPANTS:
Kathleen Schmitt, Regulatory Affairs Manager, Empi, Inc.
[redacted] Senior Staff Consultant, [redacted]

Gary L. Yingling, Esq. , Kirkpatrick & Lockhart LLP
Rebecca L. Dandeker, Esq., Kirkpatrick & Lockhart LLP

FDA PARTICIPANTS

Arthur Simone, M.D.,	Clinical Reviewer
Ravi Harapanhalli, Ph.D.,	CMC Team Leader
Jila Boal, Ph.D.	CMC Reviewer
Parinda Jani	Supervisory Project Manager

BACKGROUND

The purpose of this telecom was to clarify the Agency's comments sent to the sponsor via email on August 19, 2004 and the Agency's Information Request letter dated August 24, 2004.

1. AE reports to be sorted out using MEDRA headings and subheadings

   Dr. Simone stated that MEDRA dictionary for the AE headings/subheadings is used for the purposes of safety review of the NDA. Also, MEDRA terminology describing AE is used for writing the product label. The Agency would accept terminology of other dictionaries.

   The sponsor responded that they do not subscribe to MEDRA and do not have access to it. As far as the device part of the application is concerned, CDRH uses plain language for the AE reporting. The sponsor is willing to attempt to sort out the AEs in a manner the division is comfortable with, in plain language.

   Dr. Simone agreed to it and requested that the sponsor also submit copies of reports.

   The sponsor has submitted this information previously, however, would sort it out in the manner Dr. Simone has requested in a tabular form. The sponsor will let the Division know the timeframe.

2. CMC Comments in the letter

Drug Product Specifications (comment 1 & 2): The sponsor questioned as to why the Agency was requesting tightening of specifications as a product approved by the Agency under ANDA is going to be used in this combination. The sponsor has provided LOA for the ANDA, in case the Division has questions. If the sponsor of the ANDA agrees to tighten the specifications, they will have to submit a supplement to OGD for approval. Similarly, the device part is already approved by CDRH under 510K, and the Division was requesting additional information. The sponsor requested clarification.

Dr. Harapanhalli stated that the approved ANDA product is being used as conventional injectable product, it is not indicated for delivery by iontophoresis system. The product is currently under review and current standards for the approval of a NDA are being applied to set the specifications. The DMF holder has already revised the specifications. It would not be difficult to do the same,. The ANDA holder can submit a "Changes Being Effected" supplement to OGD.

The sponsor agreed to contact the ANDA holder to revise the specifications.

Device Information (comment 3): The sponsor questioned why the Division was requesting additional information as the device is already cleared thru 510K process for marketing by CDRH.

Dr. Harapanhalli stated that devices are cleared thru 510K for marketing not approved in the same manner as CDER approves new drugs. If the review Division needs specific information which may impact specific drug delivery system, and is not clear in the 510K application, the Division may request such information.

The requested information is needed for purposes of determining stability of the combination product and its container-closure system.

The sponsor understood the purpose of the request and will respond as soon as possible.

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
10/13/04 10:58:37 AM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-486

Trade Name: Lidopel (2% lidocaine HCl and epinephrine 1:100,000)
Generic Name:
Strengths:

Applicant: Empi, Inc.

Date of Application:	February 8, 2002
Date of Receipt:	February 11, 2002
Date clock started after UN:	October 16, 2002
Refusal to File:	December 13, 2003
RS:	September 26, 2003
Date of Filing Meeting:	November 4, 2003
Filing Date:	November 25, 2003
Action Goal Date (optional):	June 25, 2004
Clock Extension Date:	October 26, 2004

User Fee Goal Date: July 26, 2004

Indication requested: ———

Type of Original NDA: (b)(1) _____ (b)(2) ___✓___
OR
Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE:

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

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

____ NDA is a (b)(1) application OR _✓_ NDA is a (b)(2) application

Therapeutic Classification: S ___✓_____ P _____
Resubmission after withdrawal? ___no_____ Resubmission after refuse to file? _____

Chemical Classification: (1,2,3 etc.) ___4_____
Other (orphan, OTC, etc.) ___N/A_____

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

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

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity*

or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application?

  YES [NO]

  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES [NO]

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

  YES NO

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

- Is the application affected by the Application Integrity Policy (AIP)? YES [NO]
  If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? [N/A] YES NO

- Does the submission contain an accurate comprehensive index? [YES] NO

- Was form 356h included with an authorized signature? [YES] NO
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? [YES] NO

  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A [YES] NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  SAS data

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? [N/A] YES NO

- Is it an electronic CTD? [N/A] YES NO

If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? YES [NO]

- Exclusivity requested? YES, _____years [NO]
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

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

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

- Financial Disclosure forms included with authorized signature? [YES] NO
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- 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? If not, have the Document Room make the corrections.

- List referenced IND numbers: IND 54,731

- End-of-Phase 2 Meeting(s)? Date 6/30/99____ NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date 7/20/01_____ NO
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? [YES] NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? [YES] NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? [N/A] YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?

  [N/A] YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? [N/A] YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?

  [N/A] YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? [YES] NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES
  NO

- Establishment Evaluation Request (EER) submitted to DMPQ? [YES] NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? [N/A] YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 8, 2003

BACKGROUND: **UN** – February 28, 2002; **Resubmission** – October 16, 2002 [labeling revised to become **505(b)(2)** application]; **RTF**-December 13, 2002; **RTF Review Committee** – February 20, 2003; **Resubmission** – July 30, 2003, document considered minor amendment due to fileability issues by the Division on September 26, 2003; **Resubmission** – September 26, 2003, document considered a major amendment and fulfills all previous deficiencies. **Filed 11/25/03**

ATTENDEES: All reviewers; Division Director; Director, ONDC;

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Art Simone MD, PhD
Secondary Medical:	
Statistical:	Lisa Kammerman, PhD
Pharmacology:	Adam Wasserman, PhD
Statistical Pharmacology:	
Chemist:	Jila Boal, PhD
Environmental Assessment (if needed):	
Biopharmaceutical:	David Lee, PhD
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Manager:	Lisa Malandro
Other Consults:	CDRH

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

CLINICAL FILE _✓_____ REFUSE TO FILE _____

- Clinical site inspection needed: [YES] NO
- Advisory Committee Meeting needed? YES, date if known _____ [NO]
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? [N/A] YES NO

CLINICAL MICROBIOLOGY NA __✓___ FILE _____ REFUSE TO FILE _____

STATISTICS FILE ___✓___ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE __✓___ REFUSE TO FILE _____

- Biopharm. inspection needed: YES [NO]

PHARMACOLOGY NA _____ FILE __✓___ REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE __✓___ REFUSE TO FILE _____

- Establishment(s) ready for inspection? [YES] NO
- Microbiology YES [NO]

ELECTRONIC SUBMISSION:
Any comments: none

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

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

_____ No filing issues have been identified.

___✓__ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

_____
Regulatory Project Manager, HFD-

Appendix A to NDA Regulatory Filing Review

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

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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

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

   *If "**No**," skip to question 3.*

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

   Iontocaine NDA 20-530
   Octocaine ANDA 84-048

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

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

   YES [NO]

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

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

   YES NO

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? [YES] NO

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

*If "**No**," skip to question 5. Otherwise, answer part (b).*

(b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

***NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES NO

6. 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").

Different electrodes and device

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

8. 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)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO

9. 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 (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? [YES] NO

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

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

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

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

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

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

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

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

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  [YES] NO

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

  [YES] NO

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

  [N/A] YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A YES [NO]

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES NO

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND # _____ NO

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

  [YES] NO

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/s/

Lisa Malandro
10/6/04 11:11:20 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-486

INFORMATION REQUEST LETTER

9/3/04

Empi, Inc.
C/O Gary L. Yingling
Kirkpatrick & Lockhart, LLP
1800 Massachusetts Avenue NW
Suite 200
Washington, DC 20036-1221

Attn: Gary L. Yingling
Kirkpatrick & Lockhart, LLP

Dear Mr. Yingling:

Please refer to your February 8, 2002 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lidopel (2% lidocaine HCl and epinephrine 1:100,000) Topical Solution.

The Division of Medication Errors and Technical Support (DMETS) has reviewed your application (including your proposed tradename) and has the following comments. We request a prompt written response in order to continue our evaluation of your NDA.

1. DMETS does not recommend the use of the proprietary name Lidopel. In reviewing the proprietary name, the primary concerns related to look-alike and/or sound-alike confusion with Lidopen and LidoSite.
2. Revise the package insert labeling to address the following safety concerns:

3. Submit the carton and container labeling.

If you have any questions, call Lisa Malandro, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Parinda Jani
9/3/04 09:47:55 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-486

INFORMATION REQUEST LETTER

8/24/01

Empi, Inc.
C/O Gary Yingling, Kirkpatrick & Lockhart, LLP
1800 Massachusetts Avenue NW
Suite 200
Washington, DC 20036-1221

Attn: Gary L. Yingling
Kirkpatrick & Lockhart, LLP

Dear Mr. Yingling:

Please refer to your February 8, 2002 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lidopel (2% lidocaine HCl and epinephrine 1:100,000) Topical Solution.

We are reviewing the chemistry section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The following comments refer to the drug substances specifications:

   a. Provide the following revised specifications for lidocaine hydrochloride.

      (1) Individual drug-related unspecified impurity or degradation product: NMT —

      (2) Total impurity: NMT —

      (3) — NMT —

   b. Provide the following revised specifications for epipephrine.

      (1) — NMT —

      (2) — NMT —

      (3) Individual drug-related unspecified impurity: NMT —

      (4) Total known: NMT —

      (5) Total unknown: NMT —

2. The following comments refer to the Lidopel™ drug product specifications:

a. Revise the specifications for the degradation products of lidocaine and epinephrine in the drug product as follows:

(1) Individual unspecified and unidentified degradation products of lidocaine: NMT — or — whichever is lower.

(2) Individual unspecified and unidentified degradation products of epinephrine: NMT — or — whichever is lower.

3. The following comments pertain to the Dupel electrodes described in the NDA and 510(k)s.

a. Provide the names and addresses of the suppliers of the following electrode components:

(1)

(2)

b. Provide chemical composition, specifications, and certificates of analysis for the following components of the electrodes:

(1)

(2)

c. Provide certificates of analysis for the following electrode components:

d. Provide data on the and justify why specifications are not necessary for these quality attributes.

e. Provide the name and address of the pouch manufacturer for packing of the electrodes.

f. Provide the following additional specifications for the pouch container closure of the electrodes:

If you have any questions, call Lisa Malandro, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

{See appended electronic signature page}
Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
8/24/04 12:31:38 PM
For Parinda Jani

Malandro, Lisa

From: Malandro, Lisa

Sent: Thursday, August 19, 2004 3:45 PM

To: 'Dandeker, Rebecca L.'; Malandro, Lisa

Cc: Yingling, Gary L.

Subject: NDA 21-486 Lidopel request for information

Importance: High

Rebecca and Gary,
Please provide the following information pertaining to our ongoing review of the above referenced drug application. Submission of the information should be in the form of an amendment to the application.

1. For each adverse events in all of the studies involving human subjects provide the following in a single table:

    a. Subject ID and study number
    b. Subjects' age, gender, race
    c. Iontophoretic treatment (Lidopel, Iontocaine, Placebo)
    d. Iontophoretic dose administered (mA·min) - actual dose and the nominal dose
    e. Size of delivery electrode
    f. Site of iontophoretic treatment - delivery and return patch placement
    g. Adverse event - MEDDRA term and description, i.e., verbatim reported terms
    h. Site of adverse event (under delivery electrode, under return electrode, other)
    i. Severity of adverse event (mild, moderate, severe)
    j. Onset time relative to iontophoretic treatment
    k. Onset time relative to dermatological procedure
    l. Type of dermatological procedure
    m. Duration of adverse event
    n. Treatment provided for the adverse event (indicate none if none was provided)

2. If the response is to be submitted in paper form, the data should be sorted in each of the following ways:

    a. By subject
    b. By AE type, i.e., use MEDDRA headings and subheadings
    c. By treatment group (placebo, Lidopel, Iontocaine)
    d. By iontophoretic dose
    e. By study
    f. By demographic

If you have any question, please do not hesitate to contact me.
Thank you,
Lisa

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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/s/

Lisa Malandro
8/24/04 05:41:33 PM

Malandro, Lisa

From: Malandro, Lisa

Sent: Thursday, August 12, 2004 1:33 PM

To: 'Dandeker, Rebecca L.'; Malandro, Lisa

Cc: Yingling, Gary L.

Subject: NDA 21-486 Lidopel request for information

Rebecca/Gary,
Following is a request for additional information pertaining to our ongoing review of the above referenced application. Please submit a response to this request as an amendment to NDA 21-486 at your earliest convenience.

Subject 030-008 , Study #00-1-03.0 had three adverse events listed which were associated with her first treatment (she was withdrawn from the study prior to the second treatment). The first was an "upset stomach" which resolved; the second was "shoulder ache" that appeared to be related to arthritis and was still unresolved at follow-up 17 days later but was being actively treated. The third AE was "numbness at R forearm down through hand" and was also attributed to arthritis. Provide follow-up for the third AE and copies of the subject's CRFs. Indicate whether the numbness reported was new in onset or an exacerbation of an ongoing problem, a change from previous numbness (if not new onset) in terms of location, extent and/or duration, whether the numbness was temporally related to either the iontophoretic treatment or venipuncture, and what treatment, if any, was provided.

If you have any questions, please feel free to contact me.

Thanks,

Lisa

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

/s/

Lisa Malandro
8/16/04 05:30:50 PM

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: July 22, 2004

TO: Lisa Malandro, Regulatory Project Manager
Arthur F. Simone, M.D., Medical Officer
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

THROUGH: Khin Maung U, M.D., Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

FROM: Carolanne Currier
Consumer Safety Officer
Good Clinical Practice Branch 1, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-486

APPLICANT: Empi, Inc.

DRUG: Lidopel™ (Lidocaine HCl 2% and Epinephrine 1:100,000)

CHEMICAL CLASSIFICATION: 4

THERAPEUTIC CLASSIFICATION: S

INDICATION: [redacted]

CONSULTATION REQUEST DATE: 5/5/04 (Memo from Dr. Simone)

PDUFA DATE: 10/26/04

I. BACKGROUND: NDA 21-486, Lidopel (Lidocaine HCl 2% and Epinephrine 1:100,000, administered with iontophoresis), is pending approval before the Agency. The NDA was submitted by EMPI, Inc. with several different protocols identified as pivotal. During the review of [redacted]

[redacted]), so it was selected for inspection.

The [redacted] was conducted at only one study site; [redacted] with [redacted] identified as the principal investigator. The study [redacted]

II. INSPECTION RESULTS: Note there is only one inspection site.

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
/	/	/	5/5/04	7/15/04	VAI

Protocol —

Site: —— .: Data Acceptable

a. What was inspected: subjects were enrolled into the study, with one subject failing to complete the treatment. Study records examined include source documents, CRFs, drug accountability records, IRB documentation, and correspondence files. Subjects were evaluated for protocol inclusion/exclusion criteria. All source documents were compared to CRFs for selected efficacy endpoints.

b. Limitations of inspection: None

h. General observations: All subjects met inclusion/exclusion criteria. All subjects signed assent forms and all .. Drug accountability records were adequate. Study records were well-organized and mostly complete, however a few deviations from FDA regulations were noted.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

This inspection revealed that there was sufficient documentation to assure that the study subjects existed and were administered the study treatment. The protocol deviations and documentation errors do not appear to have increased the safety risk for any subject.

Carolanne Currier, CSO
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

Supervisory comment:

Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

DISTRIBUTION:
HFD-170:NDA 21-486
HFD-45/Division File / Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-46/U/Currier
HFD-46/ GCPB1 File # 11237
Cac:7/15/04:CIS Lidopel.doc

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/s/

Carolanne Currier
7/22/04 01:41:04 PM
MANGMNT ANALYST

CIS based on one inspection - Dr. John B. Rose

Khin U
7/22/04 01:43:03 PM
MEDICAL OFFICER

Malandro, Lisa

From: Malandro, Lisa
Sent: Tuesday, July 20, 2004 5:01 PM
To: 'Dandeker, Rebecca L.'; Malandro, Lisa
Cc: Yingling, Gary L.
Subject: NDA 21-486 Lidopel request for information
Importance: High

Rebecca and Gary,
Following are additional requests from the Division related to their ongoing review of the above referenced Lidopel application. Please submit your response to these requests as an amendment to NDA 21-733.

1. For Study #00-1-03.0 provide the following information for Lidopel, Iontocaine and placebo combining the results of the two treatment visits:

number and percent of subjects with successful blood draws on first attempt

number and percent of subjects with successful blood draws on second attempt

number and percent of subjects with failed blood draws after two attempts

2. For each of the venipuncture studies, provide the size of the needle(s) used, the criteria for selecting the needle size (if one size was not used throughout the study), and a table indicating subject ID, treatment, iontophoretic dose, site of treatment application, and number of attempts to successful blood draw/failed blood draw.

Please contact me if I can be of assistance.

Thank you,

Lisa

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/s/

Lisa Malandro
7/21/04 09:38:53 AM

Malandro, Lisa

From: Malandro, Lisa

Sent: Monday, June 21, 2004 4:26 PM

To: 'Dandeker, Rebecca L.'; Yingling, Gary L.

Cc: Higgins, Lorraine A.; Malandro, Lisa

Subject: NDA 21-486 Lidopel FDA Request for Information

Gary and Rebecca,
The Statistician assigned to the above referenced NDA has requested the following information. Please submit response to this request as an amendment to NDA 21-486.

Provide complete documentation on the development and validation of the VAS used in these studies.

Thank you,
Lisa

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/s/

Lisa Malandro
7/9/04 04:55:20 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

6/18/04

NDA 21-486

Empi, Inc.
C/O Kirkpatrick & Lockhart, LLP
1800 Massachusetts Avenue NW
Suite 200
Washington, DC 20036-1221

Attention: Gary L. Yingling

Dear Mr. Yingling:

Please refer to your September 26, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lidopel (2% lidocaine HCl and epinephrine 1:100,000) Topical Solution.

On June 8, 2004, we received your June 7, 2004 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 26, 2004.

If you have any questions, call Lisa Malandro, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

{See appended electronic signature page}

Parinda Jani
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

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/s/

Parinda Jani
6/18/04 01:22:59 PM

Malandro, Lisa

From: Jani, Parinda
Sent: Thursday, May 13, 2004 3:43 PM
To: 'gyingling@kl.com'
Cc: Malandro, Lisa
Subject: FW: Lidopel

Hi Gary:

I am covering for Lisa, please provide the following information ASAP.

Subject: Lidopel

1. The data sets for the Lidopel NDA are not easily manipulated or reconstructed for the venipuncture studies. Please provide within a week data tables for each of the venipuncture studies that include the following:

Subject ID, iontophoretic dose, active or placebo treatment, VAS score, satisfaction score.

These data should be analyzed to show the mean, standard deviation and ranges for the VAS and satisfaction scores for each treatment type and iontophoretic dose, e.g., the mean VAS for 20 mA-min placebo treatment was x, etc.

Submit data tables as they become available (JMP compatible preferred) rather than wait to submit the entire collection at once.

2. For study 99-07.0, provide the following as soon as possible :

Statistical analysis of the differences in VAS scores for each of the iontophoretic dose groups, i.e., for each dose group, was the difference between Lidopel treatment and placebo treatment VAS scores significantly different.

Statistical analysis of the mean differences in Satisfaction scores by dose, i.e., is there any statistically significant difference in satisfaction scores between the Lidopel and placebo treatments for each dose group, and is there a significant difference between any of the dose groups.

The final study reports do not indicate whether the studies were conducted in accordance with the Good Clinical Practice Guidelines and the Ethical Principles for Medical Research Involving Human Subjects promulgated at the 18th World Medical Association General Assembly in Helsinki and later amended.

The final study reports give no indication as to how the study was monitored or how quality assurance of the data was provided. There also was no indication that the recorded data were verified for accuracy compared with the CRFs, or that upon closeout of the study a full audit was performed. How the database was prepared, secured and verified was not stated.

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care and

Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Tel # (301) 827-7422
Fax # (301) 443-7068

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ON ORIGINAL

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/s/

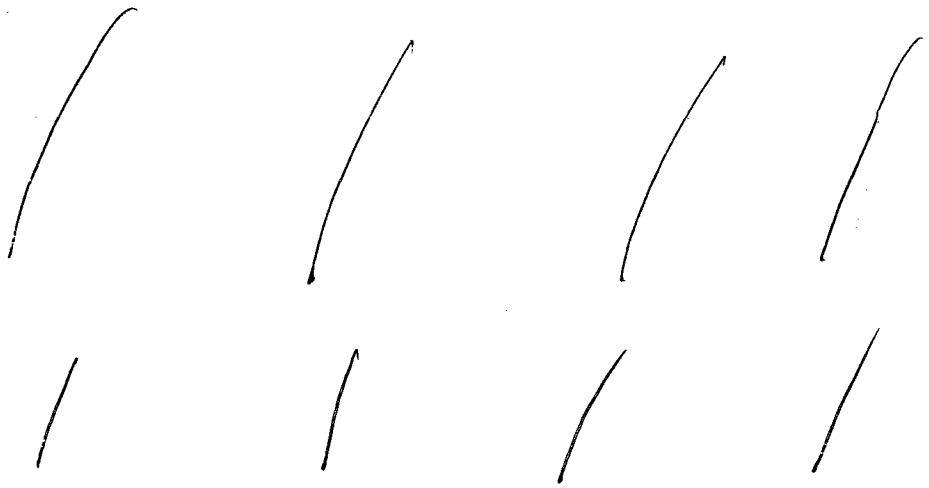
Lisa Malandro
5/19/04 05:34:35 PM

DATE March 5, 2003
FROM: K. Lee, M. D., Medical officer
FDA / CDRH / ODE / DGRND / REDB
SUBJECT: N 21486 EMPI
TO: The file

4/7/04

Final Comments by K. Lee
The Empi Dupel iontophoresis has two independent channels with each channel having a return electrode and active electrode, and with its maximal current density of — and maximum current of 4mA —. — I have no issues of safety or other issues in 510(k) K896703, K902913,K902914, K903093, K912014, K912015, K915444,K970491,K983484, K991991 of EMPI.

The sponsor had done studies comparing a predicate electrode (K912015) and modified return electrodes for the irritation of the elctrodes. In the study, each subject was treated using the same delivery electrode design (currently marketed medium Dupel (D B.L.U.E. Butterfly). The currently marketed return electrode is the Empi Buffered Iontophoretic Return Electrode. These electrodes have been cleared for marketing in the U.S. in 510(k) #K912015. All return electrodes to be used in this study consist of a — The active area of return test electrode designs 1 —) and 2 (—) are smaller than the return electrodes described in 510(k) K983484, K970491, or K912015. Since current density is inversely proportional to area designs 1 and 2 have a greater current density than a. larger size electrode. However, the current density of designs 1 and 2 is less than the maximum — described in 510(k) K983484 for the small Dupel B.L.U.E. delivery electrode. Use of the smaller sized return electrodes raise no new safety questions and are, therefore, within the scope of products defined in one of the following 510 (k) submissions: K983484, K970491, or K912015. See Appendix A for a detailed comparison of the return electrodes. The sponsor concluded that any modifications made to the test return electrodes are unlikely to impact safety. I have no any further inquiry or issues of safety. CDER should evaluate the effectiveness for each drug using the electrode and device in this NDA.



The effectiveness for each drug using the electrode and device in this NDA should be reviewed for its intended use by CDER.
Please look at the review of 510(k)s which were previously cleared by CDRH

I made summaries of the following appendix, and have no issues in the Appendices of 4-20, 21, 22, 23, 24, and 25.

Kyung Dam Lee
K. Lee M.D.
Medical officer

45 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Malandro, Lisa

From: Malandro, Lisa
Sent: Tuesday, March 23, 2004 11:15 AM
To: 'Yingling, Gary L.'
Cc: Malandro, Lisa
Subject: NDA 21-486 Lidopel - Request for Information

Contacts: Gary L. Yingling

Gary,

Following, please find several additional requests from the Division's medical officer and statistician related to their ongoing review of the above Lidopel application. Please submit response to these requests in archival format as amendment(s) to NDA 21-486.

Clinical questions and requests:

1. Was there a standardized way of conducting the "standard pinprick test," i.e., testing sites at specific locations around the lesion, pressure to be applied to the needle, or depth of penetration of the needle. Similarly, was there a standard method for conducting the "intact sensation test?"

2. For protocol 97-07.0, verify the "-7" patient satisfaction score recorded for subject #21[illegible] and indicate its significance if the correct entry is "-7." The Data Dictionary does not include a definition for this value.

3. For protocol 97-07.0, provide verification that subject #102 had a VAS score of "0." If this was the case, provide an explanation for the adverse event recorded as "pain (when base of biopsy cut)."

4. Provide the 2nd amendment for protocol 99-02.0.

5. Create a table of the VAS and Global Satisfaction Scores for all studies, include protocol #, subject ID dermatological procedure, patch size, iontophoretic dose and test drug used (describe placebo, e.g., iontophoretic dose and presence or absence of drug).

6. Did the composition of the patches change at any point during the clinical studies? If so, identify the studies conducted with the new formulation and provide information on how these changes would be expected, or not expected, to impact the delivery of drug product under the proposed conditions of use.

7. In Appendix 8-3 on page 17, in the Conclusions section, number 2 states that there was "only one minor observation" by way of adverse events for the 40 mA·min/active treatment group and that the placebo group had six events. The abridged data set indicates 13 AEs for the 40 mA·min and 20 for the placebo group with 80 mA·min. Additionally, the data table includes a 40 mA·min/placebo treatment group as having 10 AEs (such a treatment group does not exist in the protocols), and there are no AEs listed for either the 60 mA·min active treatment (in phase I and II of the study) or placebo (in phase II of the study) groups. Provide an explanation of the discrepancy and indicate where the appropriate AE data may be found, or if necessary, provide the AE data.

Statistical requests:

1. Explain in detail the randomization methods used for each study. Provide the randomization scheme and codes used for each study. For further information, see Format and Content of the Clinical and Statistical Sections of an Application which is located at http://www.fda.gov/cder/guidance/statnda.pdf.

2. **VAS**
   a. Provide complete documentation on the development and validation of the VAS used in these studies.
   b. Describe the reading level targeted by "Please rate any degree of discomfort experienced during the blood draw procedure by placing a mark on the line below."

   c. Explain in detail the methods used to implement the visual analogue scale. For example, include a discussion of whether the subject read the instructions and then completed the VAS, or whether the observer read the instructions to the subject, who then completed the VAS.
   d. Explain the methods used to translate the information on the VAS into useable data.
   e. For each subject in these studies, provide copies of the actual VAS as completed by each subject.

3. Explain why neither the CFR nor the protocol contains a copy of the VAS.

4. **In Study 99-07-0,** describe the randomization procedure used to determine which arm first received the venipuncture procedure.

5. **For Study 001-1-03.0:**
   a. Describe the Iontocaine placebo.
   b. This study uses an electrode size (10.1 cm^2) that differs from the size (8.1 cm^2) used by the other studies that assessed 20 mA? min. Provide a rationale for the selection of 10.1 cm^2 and its impact on the assessment of safety and efficacy of Lidopel.
   c. Describe how blinding was preserved. Because two different devices were used, the investigator and, possibly, the subject knew which treatment (Lidopel or Iontocaine) the subject was receiving.

If you have any questions regarding these requests, please do not hesitate to contact me.
Thanks
Lisa

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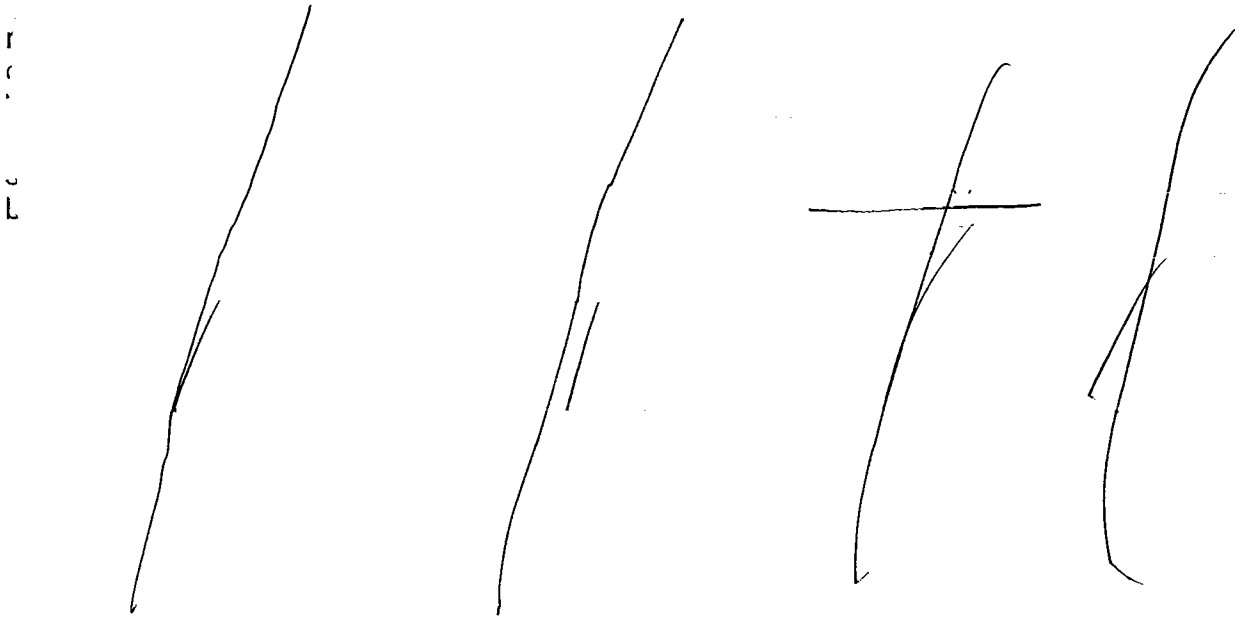
/s/

Lisa Malandro
3/23/04 07:36:36 PM

Malandro, Lisa

From: Malandro, Lisa
Sent: Thursday, March 18, 2004 6:35 PM
To: 'Yingling, Gary L.'
Subject: RE: Empi NDA 54-731

Hi Gary,
In response to both of your messages,
1. Regarding the labeling:



2. Regarding the Safety Update: Empi should refer to 21 CFR 314.50(d)(vi)(b). More specific requirements for format and content can be found in the DHHS document "Guideline for The Format and content of the Clinical and Statistical Sections of New Drug Applications" dated July 1988, Page 45. Please note that this safety update is nearly two months overdue. Empi should be aware that delay in the submission of this information to the Division is compromising the review of this application.

If you have any further questions regarding the review of this application, please do not hesitate to contact me.
Thanks,
Lisa

-----Original Message-----
From: Yingling, Gary L. [mailto:gyingling@kl.com]
Sent: Wednesday, March 17, 2004 12:25 PM
To: Lisa Malandro (E-mail)
Subject: Empi NDA 54-731

Empi submitted an amendment to the NDA yesterday which responds to the questions sent by email except for the labeling question.

Gary L. Yingling
Kirkpatrick & Lockhart, LLP
1800 Massachusetts Ave, NW
Washington, DC 20036
(202) 778-9124 (Direct)
(202) 778-9100 (Fax)
http:\\www.kl.com

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/s/

Lisa Malandro
3/23/04 07:34:33 PM

Malandro, Lisa

From: Malandro, Lisa
Sent: Friday, March 05, 2004 3:18 PM
To: 'Yingling, Gary L.'
Cc: Malandro, Lisa
Subject: NDA 21-486 Lidopel

Contacts: Gary L. Yingling

Gary,
Please have the Sponsor submit a copy of Protocol Amendment #2 from study #99-020 as an amendment to their NDA. The protocol amendment has been ommitted from the application.
Thanks,
Lisa Malandro

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/s/

Lisa Malandro
3/5/04 03:26:06 PM
CSO

Malandro, Lisa

From: Malandro, Lisa
Sent: Friday, February 13, 2004 2:05 PM
To: Malandro, Lisa; 'Yingling, Gary L.'
Subject: RE: NDA 21-486 Lidopel Information request

Importance: High

Gary, This is a revised version of the copy I just forwarded to you. My computer crashed mid-edit and this was sent off without our revisions.
Please see below for revised requests.

-----Original Message-----
From: Malandro, Lisa
Sent: Friday, February 13, 2004 1:38 PM
To: 'Yingling, Gary L.'
Subject: NDA 21-486 Lidopel Information request

Gary,
Thank you for sending the desk copy of the labels. However, these must be submitted formally to the NDA as hard copies, as well.

The Medical Officer for this application has requested the following information. Response to these requests should be submitted as an amendment to the NDA as soon as possible so that the review of the application can progress.

1. Provide a list of which studies conducted by Empi were completed under Good Clinical Practice Guidelines. Also provide a list of which studies were completed in accord with the Helsinki Agreement for Ethical Principles for Medical Research Involving Human Subjects.

2. Provide a table for each protocol that lists each protocol deviation along with the patient identification and assigned treatment group.

3. Provide the following information for each clinical trial. Providing this information in a tabular format (such as the example below) would be most helpful.

Subject Status	Treatment A	Placebo	Total
Enrolled	n (%)	n (%)	n (%)
Randomized			
Safety Population (Received treatment)			
Intent-to-Treat (ITT) Population			
Completed Study			
Prematurely Discontinued Study			
Problem A			
Problem B			

ETC.			

4. The patient identifications listed in the protocol deviation section of study 97-07.0 do not correspond to subject IDs used in the SAS data files. Provide the correct ID.

5. Identify which subjects in 97-07.0 underwent dermatological procedures and requested additional anesthesia. Identify those who were not assessed for VAS and subject satisfaction. Provide explanations for why these subjects were not assesseed.

6. Provide VAS and subject satisfaction forms which should have been part of the CRFs for study 97-07.0 (and others if applicable) and include explanation for why they were not included initially.

7. Provide annotated CRFs for all clinical trials.

If you have any questions, please do not hesitate to contact me.
Thanks,
Lisa

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/s/

Lisa Malandro
2/23/04 04:11:20 PM
CSO

Malandro, Lisa

From: Malandro, Lisa
Sent: Tuesday, February 03, 2004 4:30 PM
To: 'Yingling, Gary L.'
Cc: Malandro, Lisa
Subject: NDA 21-486 Clinical Information Request

Importance: High

Gary,
The Medical Officer reviewing this application has requested the following information.

1. Provide the full, final study report for the safety trial that was conducted to compare the two return patch sizes (referenced in Section 8, Pages 16 & 17 of the NDA).

2. Provide any other study reports and/or data that were referenced in, but not included in the NDA.

3. Specify which of the patches are to be used with the drug product and, if more than one delivery patch or one return patch is to be used.

4. Provide a description of the "Intact Sensation to Light Touch" test that is discussed in Appendix 8-2 on Page 45 of the NDA.

Response to this request should be submitted as an amendment to NDA 21-486.

If you have any questions, please feel free to contact me.
Lisa

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/s/

Lisa Malandro
2/3/04 04:28:56 PM
CSO

For Consulting Center Use Only:
Date Received: 12/10/03
Assigned to: Dr. Kevin Lee
Date Assigned: 12/10/03
Assigned by: Ted Stevens
Completed date: 4/7/04
Reviewer Initials: KKL
Supervisory Concurrence: TRS

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: Jila Boal, Ph.D.
Requesting Reviewer's Concurring Supervisor's Name: Ravi Harapanhalli, Ph.D.
Building/Room #: PKLN 9B-45
Phone #: 301-827-7436
Fax #: 301-443-7068
Email Address: boalj@cder.fda.gov
RPM/CSO Name: Lisa Malandro (malandrol@cder.fda.gov)
(consult initialed by PJ, CPMS, 11-25-03)

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: 11-24-03

Requested Completion Date: April 30, 2004

Submission/Application Number: N 21-486
(Not Barcode Number)

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

Submission Receipt Date: 9-26-03

Official Submission Due Date: 6-25-04 (Division Goal Date
7-25-04 (PDUFA Goal Date)

Name of Product: **Lidopel (2% lidocaine HCl and epinephrine 1:100,000** Name of Firm **Empi, 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 X 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 Drug (NDA 21486):

Lidopel™ is indicated . 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 ling

. 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.

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

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

Areas requiring CDRH Consult:

The labeling states that 'ed.
Empi states that they will submit revised labeling for the device and electrodes to the CDRH upon approval of the NDA. We request that the following sections described in Volume 1.7 of the NDA be specifically reviewed by the CDRH with regard to the design controls, electrical and electrochemical specifications of the Dupel™ Iontophoresis System and the Dupel Iontophoresis Electrodes as they relate to the iontophoretic delivery of Lidopel™.

If you have any questions please contact the CMC reviewer, Dr. Jila Boal at 301-827-7436.

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: **X** Consultative Review □ Collabortive Review

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

12/9/03

NDA 21-486

Empi, Inc.
C/O Kirkpatrick & Lockhart, LLP
1800 Massachusetts Avenue NW
Suite 200
Washington, DC 20036-1221

Attention: Gary L. Yingling

Dear Mr. Yingling:

Please refer to your February 8, 2002, new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lidopel (2% lidocaine HCl and epinephrine 1:100,000) Topical Solution.

We also refer to your submission dated September 26, 2003.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b)(2) of the Act on November 25, 2003, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

> The database contains a fairly small number of exposures to Lidopel at each dose tested. The adequacy of the database for a determination of safety and efficacy at the appropriate dose(s) will be the subject of ongoing review.

We are providing the above comment to give you preliminary notice of a potential review issue. 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 have any questions, call Lisa Malandro, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Division Director
Division of Anesthetic, Critical Care
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
12/9/03 06:17:13 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

10/16/03

NDA 21-486

Empi, Inc.
C/O Gary L. Yingling
Kirkpatrick & Lockhart, LLP
1800 Massachusetts Avenue NW
Suite 200
Washington, DC 20036-1221

Dear Mr. Yingling:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act in response to our December 13, 2002, refusal to file letter for the following:

Name of Drug Product: Lidopel (2% lidocaine HCl and epinephrine 1:100,000) Topical Solution
Review Priority Classification: Standard (S)

Date of Application: September 26, 2003

Date of Receipt: September 26, 2003

Our Reference Number: NDA 21-486

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 25, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 26, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

{See appended electronic signature page}

Lisa Malandro
Regulatory Project Manager
Division of Anesthetic, Critical Care
and Addiction Drug Products, HFD-170
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lisa Malandro
10/16/03 05:56:06 PM

MEMORANDUM OF TELECONFERENCE

DATE: September 26, 2003

APPLICATION NUMBER: NDA 21-486, Lidopel (2% lidocaine HCl and epinephrine 1:100,000) Topical Solution

BETWEEN:

Name: Gary Yingling, Kirkpatrick & Lockhart, LLP
Phone: 202-778-9124
Representing: Empi, Inc.

AND

Name: Lisa Malandro, Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: Decision regarding July 29, 2003 submission to NDA 21-486

BACKGROUND: In teleconferences held on September 4 and 23, 2003, the Sponsor was informed of deficiencies that the Division had identified during the review of the July 29, 2003 submission to NDA 21-486. These deficiencies included formatting issues in data sets and lack of a comprehensive table of contents linking the appropriate sections of the original submission with those of all subsequent submissions. The Sponsor was informed that these items were filing issues and in order for this submission to be considered as a complete response to the refuse-to-file action (December 13, 2002) they would have to be received and reviewed by the Division prior to September 26, 2003.

TELECONFERENCE: As of the afternoon of September 26, 2003, the Division had not received the materials necessary to consider the July 29, 2003, submission a complete response to the deficiencies outlined in the refuse-to-file letter (December 13, 2002). In a teleconference held between the above referenced individuals, the Division indicated that there was not adequate time for the Division to thoroughly review these materials should they be submitted and, therefore, the Division had made the decision to consider the July 29, 2003 submission as a minor amendment to NDA 21-486. The Division stated that the receipt of these materials would be considered as a complete response to the refuse-to-file and that their receipt would initiate the review clock.

_____

Lisa Malandro
Regulatory Project Manager

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/s/

Lisa Malandro
10/2/03 04:23:02 PM
CSO

MEMORANDUM OF TELECON

DATE: September 16, 2003

APPLICATION NUMBER: NDA 21-486 (Lidopel)

BETWEEN:

Name: Gary L. Yingling, Kirkpatrick & Lockhart, LLP
Phone: 202-778-9124
Representing: Empi, Inc

AND

Name: Bob Rappaport, M.D., Division Director
Sara E. Stradley, Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products,
HFD-170

SUBJECT: The purpose of this teleconference was to clarify points from the September 4, 2003 teleconference.

Dr. Rappaport reiterated that three things discussed during the September 4, 2003 teleconference need to be resolved before the application can be filed.

- The ISS should be integrated unless the Sponsor can provide a scientific rationale explaining why the data cannot be integrated.
- The Sponsor must provide a comprehensive table of contents.
- The Sponsor must fix the illegible data points even if the format prevents the Division from manipulating the data. The data format should be consistent throughout the ISS.

Gary Yingling stated they were surprised with the points raised in the September 4, 2003 teleconference. Based on a discussion with the Division during the April 2, 2003 telecon, the Sponsor was under the impression that their submission would be acceptable based on comments made by the Division. Thus they filed the application on July 29, 2003, and thought the issues were resolved.

Dr. Rappaport stated that there was apparent miscommunication at the April 2, 2003 teleconference as the discussion was centered on improvements to the data and that is a different issue from an integrated ISS. Dr. Rappaport again stated that if the Sponsor cannot integrate the data than the Sponsor should submit a rationale which would resolve one of the filing issues. It was unclear from Gary Yingling if the February 25, 2003 submission contained a rationale. Dr. Rappaport reminded the Sponsor that the rationale may be unacceptable to the Division and could lead to a non approvable action for the application.

Gary Yingling stated he would talk with the Sponsor, clarify these issues with them and contact the Division concerning their plans to resolve these filing issues.

Sara E. Stradley
Regulatory Project Manager

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/s/

Sara Stradley
9/30/03 04:20:15 PM
CSO

MEMORANDUM OF TELECON

DATE: September 4, 2003

APPLICATION: NDA 21-486

BETWEEN:

Name: Kathleen Schmitt, Empi

Rebecca Danekei, Kirkpatrick and Lockhart
Gary Yingling, Kirkpatrick and Lockhart

AND

Name: Bob Rappaport, M.D., Acting Division Director
Nancy Chang, M.D., Medical Team Leader
Art Simone, M.D., Medical Reviewer
Sara Stradley, M.S., Regulatory Project Manager
Division of Anesthetic, Critical Care and Addiction Drug Products

SUBJECT: The purpose of this telecon was to discuss problems with the electronic submission dated August 12, 2003.

The Division had previously stated it was having problems interpreting the contents of the data sets, specifically, DATA9707, DATA9902, DATA9914 and DATA00103. The problems encountered included the following:

AE_TIME values were not meaningful in DATA9707 and DATA9902.
In DATA9914 some data were meaningful; however, the "2" value used in RES_TIME and AE_TIME was not.
RES_DATE values of "01/03/1960" were not meaningful.
RES_TIME values and DURADAYS values were not meaningful.

Since that time, the Division was able to locate the appropriate data dictionaries and resolve most, but not all of these problems. The Sponsor clarified that some of the still uninterpretable numbers were SAS formatted date/time values that were expressed in seconds past midnight. Other data that were expressed as military time were formatted as character strings. The Sponsor stated that the Division should be able to re-program the data sets. However, the Division stated that the data sets should have been submitted in a legible format consistent with that listed in the data dictionaries, and that it is the sponsor's responsibility to program the data sets in a manner that is legible and reviewable. The current format prevents the reviewer from analyzing times to onset, resolution times and durations. It would be highly preferable if the data could be formatted to allow such data analysis, but at a minimum, the primary data must be legible

and interpretable without the need for further manipulation or programming by the reviewer.

The Division also requested a comprehensive table of contents. The current submission refers to certain sections of the original February, 2003 submission and updates/replaces others, but there is no single updated table of contents linking the appropriate sections of the original submission with those of all subsequent submissions. The lack of a comprehensive table of contents is a filing issue.

The Division also noted that the lack of an integrated safety database that merged all of the databases. The Sponsor stated they were unable to provide this as it would constitute a monumental task and that some of the data were not compatible. The Division stated that to the extent scientifically feasible, a comprehensive database of all safety data should be included as part of the ISS. Scientific justification for excluding particular studies could be offered, but where possible, all data should be integrated. The Division noted that combining the safety data from all studies requires a significant amount of time and results in a substantial volume of material, but this is a requirement of all sponsors.

The Sponsor stated that they tried to make review of the NDA easier for the FDA by submitting the electronic version of the datasets, but that an electronic integrated safety database may not be feasible. The Division stated that they have offered several times in the past to work with the Sponsor with regards to what would be required in the NDA submission, regardless of format, including an invitation to come to the Agency and work directly with the review team. The Sponsor stated that they thought the best way to help the Division was to submit the information electronically instead of a paper copy. The Division reiterated that an electronic submission was strongly encouraged but not required. The Division also reminded the Sponsor that they should have taken the time to fix these problems, especially after the previous refuse to file.

The offer to come to the Agency and work directly with the review team was again extended, but the Sponsor stated they would regroup at this time.

Meeting minutes prepared by Sara Stradley
Concurred by

Parinda Jani 9/22/03
Bob Rappaport 9/22/03
Nancy Chang 9/17/03
Art Simone 9/17/03

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/s/

Sara Stradley
9/23/03 09:01:02 AM
CSO

MEMORANDUM OF TELECON

DATE: April 2, 2003

APPLICATION NUMBER: 21-486, Lidopel® (2% Lidocaine HCl and Epinephrine 1:100,000) topical solution

BETWEEN:

Name: Gary L. Yingling, Kirkpatrick & Lockhart, LLP

Phone:

Representing: Empi, Inc.

AND

Name: Lisa Malandro, Regulatory Project Manager
Stella Grosser, PhD, Statistician
Lex Schultheis, MD, Medical Officer
Nancy Chang, MD, Medical Team Leader

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

SUBJECT: Division's Response to Data Submitted in Response to the Refuse to File Action

A teleconference was held at 9:30 am on April 2, 2003, in order for the Division and representatives of Empi, Inc. to discuss corrected data that were submitted on February 25, 2003 (IND 54,731; SN-032) to the Division for review following the Refusal to File action (December 13, 2002).

The Division stated that there were significant improvements made to the data. On initial review, the data now appear to meet minimum filing. However, the Division noted the following:

1. Some data fields are still populated with bullets. The Division requests that these fields are populated with an appropriate descriptor (i.e., if data is missing state that it is missing). The Division also suggested that if a field can be filled, it should be.
2. Adverse event times are missing. The Sponsor should improve or clarify these data prior to resubmission of the NDA and also provide fields describing variables such as onset and duration of events. Alternatively, the fields may be formatted for calculations of elapsed time.
3. The adverse event tables meet the minimum requirements, however, they can be combined into a more comprehensive file across studies since each table contains only a few broad categories.

The Division suggested that the Sponsor take this opportunity to polish the data as much as possible prior to resubmission in order to ease review so that the Division can concentrate on the science.

Lisa Malandro
Regulatory Project Manager

Nancy Chang, MD (concurrence)
Team Leader, Anesthetics

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/s/

Lisa Malandro
4/25/03 10:43:32 AM
CSO

Nancy Chang
4/25/03 11:38:35 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

12/13/02

NDA 21-486

Empi, Inc.
C/O Gary L. Yingling
Kirkpatrick & Lockhart, LLP
1800 Massachusetts Avenue NW
Suite 200
Washington, DC 20036-1221

Dear Mr. Yingling:

Please refer to your February 8, 2002, new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Lidopel (2% lidocaine HCl and epinephrine 1:100,000) Topical Solution.

You were notified in our letter dated February 28, 2002, that your application was not accepted for filing due to non-payment of fees.

Subsequently, in our letter dated September 26, 2002, you were notified of FDA's User Fee Determination for this NDA.

Your October 16, 2002, response to our September 26, 2002, letter was found satisfactory and you were notified on October 22, 2002, that your application was acceptable.

After preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

1. The current integrated summary of safety (ISS) does not present data in a reviewable format. The table that presents adverse events across studies does not contain key information required for the review of this integrated data set. For example, there is no information included about patient demographics, treatment group, extent of exposure or temporal relationship between treatment and adverse event. Nor has information been provided regarding severity, duration, outcome, and action taken for each adverse event.

2. There is no presentation of data analyzed by gender, race, age, and other relevant subgroups in the integrated summary of efficacy (ISE) or ISS. There is text describing the conclusions of your analysis, but the data are not included.

3. The clinical database is not reviewable as submitted. Even on superficial review, the database is scattered with entries that are illogical or undefined. Many of the column headers are undefined or do not correspond to those defined in the data definition tables.

There are also instances in which data entries are truncated. Finally, there is at least one instance in which data appear to be missing entirely, e.g. a particular patient does not appear in certain data tables for a study.

In addition, the format of the electronic database is very difficult to review. For further details, refer to the guidance documents "Guidance for Industry: Providing Regulatory Submissions in Electronic Format —General Considerations" and "Guidance for Industry: Regulatory Submissions in Electronic Format; New Drug Applications" which are available on our website, along with the document "Example of an Electronic New Drug Application Submission". http://www.fda.gov/cder/regulatory/ersr.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference.

If you have any questions, call Lisa Malandro, Regulatory Project Manager, at (301) 827-7407.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Acting Division Director
Division of Anesthetics, Critical Care
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
12/13/02 02:53:12 PM

MEMORANDUM

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

DATE: December 11, 2002

TO: NDA 21-486 File

FROM: Lisa Malandro, Regulatory Project Manager

SUBJECT: **Teleconference informing Empi, Inc. of Division's intentions to Refuse to File**
NDA 21-486
Lidopel (2% lidocaine HCl and epinephrine 1:100,000) Topical Solution

Response to: Fax of letter received from the Sponsor dated December 11, 2002 (Please note that this letter was received in triplicate throughout the day, each copy with minor revisions)

Attendees representing Empi Inc.:

Donald Stone	Kirkpatrick & Lockhart, LLP
Gary Yingling	Kirkpatrick & Lockhart, LLP
/	/
H. Philip Vierling	Empi, Inc

FDA attendees:

Lisa Malandro	Regulatory Project Manager
Parinda Jani	Chief, Project Management Staff
Stella Grosser, PhD	Statistical Reviewer
Nancy Chang, MD	Anesthetics Team Leader
Bob A. Rappaport, MD	Acting Division Director

A teleconference was held at 3:30 pm on December 11, 2002, between representatives of Empi, Inc. and the FDA Division of Anesthetics, Critical Care and Addiction Drug Products (as listed above) in order to discuss the letter which was received by fax in the Division at approximately 1:00 pm.

The Sponsor was informed that there were two major flaws in their application that had not been corrected which would not allow the application to be filed. .

1. Safety and effectiveness data need to be presented by subgroups. A discussion (text beginning on page 150 of Section 8) summary is not sufficient to fulfill this regulatory

requirement.

2. The Division is concerned about the quality of the data as well as its legibility and reviewability. The Division stated that the issues appear to be systemic (i.e. throughout the entire electronic database) and questions whether the data has undergone a quality control process prior to its submission to the Agency.

The Division stated that they feel that under 21 CFR 314.101(d)(3) the application is incomplete due to uninterpretable data. The Division also stated that their position is supported by 21 CFR 314.50(c)(5)(VI)*a* since not all of the data required is available in the integrated summary of safety (ISS).

Dr. Rappaport stated that he believed these items could have been resolved quickly and was surprised that the letter stated that the items could not be submitted to the Division for 45 days. He stated that the Division has seen these types of issues before and are more than happy to work with the company to correct them. The Division encouraged the Sponsor to come to the Agency and meet with the review team in order to discuss the problems so that the next filing will go smoothly.

The Sponsor questioned if a quicker turn around time would appease the Division. The Division stated that due to the PDUFA timelines, it would not be acceptable to the Division to receive these documents during the review time period, thus, shortening the time period in which we have to review the application.

The Division stated that the Sponsor would receive a refuse to file letter by the close of business on Friday, December 13, 2002. The Sponsor was informed that they could resubmit at any time, however, the Division strongly recommended that they meet with the review team and look at the electronic database together prior to resubmission.

The Sponsor questioned whether the letter would itemize all the issues. The Division replied that the regulatory requirements would be itemized in a global sense, however, each individual mistake would not be listed. Additionally, the Division stated that there are many smaller issues which should be discussed. The Division encouraged the Sponsor to access application reviews and electronic submissions guidances which are available on the FDA website in order to better understand the review process.

The Sponsor stated that they would contact the Division in the beginning of January to arrange a conference call to discuss the status of the application and the Sponsor's intentions for resubmission.

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/s/

Lisa Malandro
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CSO

MEMORANDUM

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

DATE: December 9, 2002

TO: NDA 21-486 File

FROM: Lisa Malandro, Regulatory Project Manager

SUBJECT: **Teleconference regarding NDA filing deficiencies**
NDA 21-486
Lidopel (2% lidocaine HCl and epinephrine 1:100,000) Topical Solution

Attendees representing Empi Inc.:

Donald Stone	Kirkpatrick & Lockhart, LLP
Gary Yingling	Kirkpatrick & Lockhart, LLP

FDA attendees:

Lisa Malandro	Regulatory Project Manager
Lex Schultheis, MD	Clinical Reviewer
Stella Grosser, PhD	Statistical Reviewer
Nancy Chang, MD	Anesthetics Team Leader

A teleconference was held at 4:30 pm on December 9, 2002, between representatives of Empi, Inc. and the FDA Division of Anesthetics, Critical Care and Addiction Drug Products (as listed above). During this teleconference, representatives of Empi, Inc. were informed that the Division had identified several issues with NDA 21-486 during the initial filing review which included deficiencies required by regulation, as well as several other deficiencies which concerned the Division. The sponsor was further informed that some of these issues could potentially be considered filing issues if they could not be resolved prior to the filing deadline.

The Division cited the following regulatory requirements that were not included in the NDA as submitted:

1. Integrated safety summary data tables (that which was included in the NDA was lacking several key elements such as patient demographics, treatment group, extent of exposure, temporal relationship between treatment and adverse event, or severity, duration, outcome, and action taken, if any, of each adverse event).

2. Integrated safety and efficacy data by race, gender and age.

The Division also cited several data "legibility" issues and examples:

1. Column headers that do not match data definition tables or which are not defined on data definition tables.

2. Truncated text

3. Entries that on their face appear to be illogical or incorrect. These included data entries that included a seemingly impossible number of significant digits (VAS scores and temperatures), dates such as 1899 and 2028, and entries such as –7 that were not defined.

The Division stressed their concern about the interpretability and reliability of the data, based on the number of findings they had already accumulated during this cursory review. The Division informed the Sponsor that the filing deadline for this application would occur on Friday, December 13, 2002. The Division suggested that the elements required by regulation be addressed and the electronic database be subjected to a complete quality control (QC) process for legibility and accuracy, and that this QC process should be documented for Agency review. A submission was requestedby the close of business on Wednesday, December 11, 2002, if the sponsor wished to have the submission considered and reviewed prior to the filing decision. Additionally, the Division stated that the electronic database was very difficult to work with and requested that the Sponsor refer to the guidance for electronic submissions.

The Sponsor indicated that they would not be able to provide the Division with the documents required by the regulations by Wednesday, December 11, 2002, but would get back to the Division with their intentions by Wednesday.

Additionally, the Sponsor stated that they were concerned that many of these issues could have been addressed had the Division informed them earlier.

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/s/

Lisa Malandro
12/13/02 01:39:27 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

10/22/02

NDA 21-486

Empi, Inc.
C/O Gary L. Yingling
Kirkpatrick & Lockhart, LLP
1800 Massachusetts Avenue N.W.
Suite 200
Washington, D.C. 20036-1221

Dear Mr. Yingling:

Please refer to your new drug application (NDA) dated February 8, 2002, received February 11, 2002, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Lidopel (2% lidocaine HCl and epinephrine 1:100,000) Topical Solution.

You were notified in our letter dated February 28, 2002, that your application was not accepted for filing due to non-payment of fees.

Reference is also made to Agency's letter dated September 26, 2002, in which you were notified of FDA's User Fee Determination for this NDA. In response to the Agency's September 26, 2002, letter, you have revised your labeling and deleted [redacted] indication [redacted]

This is to notify you that the response received is satisfactory, and your application has been accepted as of October 16, 2002.

The review priority classification for this application is standard (S).

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 15, 2002, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be August 16, 2003, and the secondary user fee goal date will be October 16, 2002.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Ms. Lisa Malandro at (301) 827-7410.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and Addiction
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
10/22/02 12:00:25 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 26 200

Gary L. Yingling
Donald R. Stone
Kirkpatrick & Lockhart LLP
1800 Massachusetts Avenue, N.W.
Suite 200
Washington, D.C. 20036-1221

RE: User Fee Determination for NDA 21-486, Lidopel

Dear Mr. Yingling and Mr. Stone:

This responds to your letter of April 18, 2002, concerning the applicability of user fees under the provisions of the Federal Food, Drug, and Cosmetic Act (the Act)[1] for Empi, Inc.'s (Empi) new drug application (NDA) for Lidopel (2% lidocaine hydrochloride and epinephrine 1:100,000). For the reasons described below, the Food and Drug Administration (FDA) believes that Empi's application for Lidopel is subject to an application fee.

I. Your Request

You state that NDA 21-486, Lidopel, was submitted to the Agency on February 8, 2002. The appropriate user fee was not received for this application and the NDA was considered incomplete and not accepted for filing.[2] Since the submission of the NDA, FDA has been reviewing the applicant's claim for exemption from user fees. You further state that you were asked several questions to which you have responded. In your letter to me, you included your responses, dated March 5, 2002, and March 13, 2002, to Ms. Victoria Kao, Project Manager, Division of Anesthetic, Critical Care, and Addiction Drug Products with whom you have been discussing this matter.

II. Is Empi's Lidopel Application Subject to a Fee?

A. When is a 505(b)(2) Application Subject to a Fee?

You state that to be eligible for a user fee exemption, a 505(b)(2) NDA must reference a drug product that contains the same molecular entity and same indication for use as a drug product that has already been approved by FDA. You assert that Empi's application meets these conditions.

Under section 736(a) of the Act, a human drug application submitted on or after September 1, 1992, is subject to an application fee. As defined in section 735(1)(B) of the Act, the term "human drug application" includes an application for

[1] See sections 735 and 736 of the Act (21 U.S.C. 379g and 379h).
[2] See FDA's letter dated February 28, 2002.

approval of a new drug submitted under section 505(b)(2) after September 30, 1992, which requests approval of –

(i) a molecular entity which is an active ingredient (including any salt or ester of an active ingredient), or

(ii) an indication for a use,

that had not been approved under an application submitted under section 505(b).

If either condition (i) or (ii) above applies, a 505(b)(2) application is subject to an application fee.

B. Does Lidopel meet the first condition?

The first condition for an application to be termed a human drug application is that the application must request approval of a molecular entity which is an active ingredient (including any salt or ester of an active ingredient) that had not been approved under an application submitted under section 505(b). Empi's 505(b)(2) application for a drug product containing both lidocaine and epinephrine would not be subject to an application fee under the first condition because Iontocaine, approved December 21, 1995, is the same combination of molecular entities as Empi's proposed product.

Both lidocaine and epinephrine have been approved under section 505(b) as active ingredients in NDAs. Both active ingredients were approved under several NDAs, including, as you pointed out, NDA 20-530, Iomed's Iontocaine. Because both molecular entities are active ingredients approved in applications submitted under section 505(b), Empi's 505(b)(2) application for a drug product containing both lidocaine and epinephrine would not be subject to an application fee under the first condition.

C. Does the Lidopel application request a new "indication for a use"?

1. What does "indication for a use" mean?

The second condition for an application to be termed a human drug application is that the application must request approval of a new "indication for a use." You state that FDA's interpretation of the term "indication for use" is overly broad. You also state that FDA contradicts itself by asserting that "indication for use" means "all labeling statements" while you interpret FDA's regulations to specifically distinguish between the "indication" labeling statement and other labeling statements.

The Agency believes that the term Congress used, "indication for a use," as stated in section 735(1)(B) of the Act, is broader than the term "indication for use," as defined in your letter. We note that Congress could have used the term "indication" or "indication for use," but instead chose the term "indication for a use." In addition, a review of the

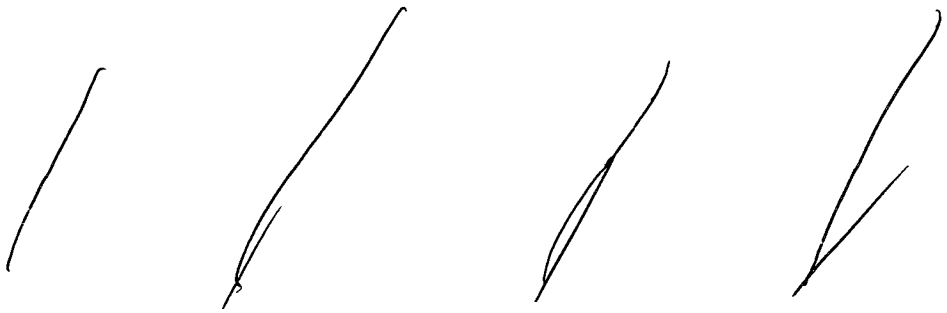
legislative history[3] leads to a broader interpretation of the term "indication for a use" than you are advocating. The pertinent portion of the legislative history is as follows:

> The change, made after the bill was reported by the committee but which is in the bill, would limit the section 505(b)(2) applications included within the definition of "human drug application" — section 735(1)(B), as added by section 3 — to applications that request approval of first, [a] molecular entity which is an active ingredient or second, an indication for a use that had not been approved under an application submitted under section 505(b). The committee intends that the term "indication" be given the meaning that it is given in the FDA's regulations, 21 CFR 201.57(c), 1992. This term would include an Rx to OTC switch. User fees would not be required for any other new drugs approved under section 505(b)(2).

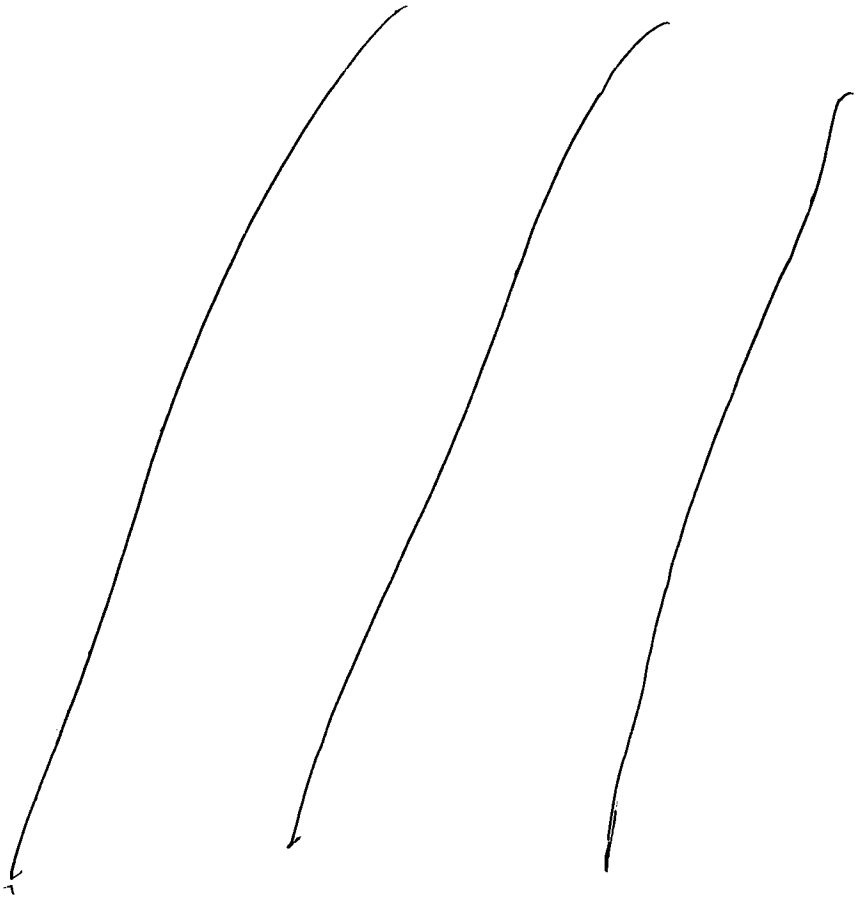
The framers of the user fee statute could have easily mimicked the term "Indications and Usage" as used in 21 CFR 201.57(c) rather than refer to the term "indication for a use." However, the legislative history makes clear that a broader reading should be used by stating that the term "indication" be given the meaning that it is given in FDA's 1992 regulations at 21 CFR 201.57(c). Because Congress did not specify a particular portion of 21 CFR 201.57(c), but instead referenced the entire section, FDA believes that substantive changes to any part of the labeling referenced in 21 CFR 201.57(c) would result in a new "indication for a use."

Further, Congress mentioned an Rx-to-OTC switch as an example of a broad interpretation of "indication for a use." In an Rx-to-OTC switch, the actual indication remains the same (e.g., treating hypertension); however, the "indication for a use" would change (Rx-to-OTC). Therefore, FDA believes a plain reading of the statute as supported by the legislative history leads to the conclusion that any change in the package insert labeling for a 505(b)(2) application that would fall under 21 CFR 201.57(c) would be a new "indication for a use." Based on this interpretation, we analyze below whether Lidopel meets this definition of "indication for a use."

2. **Does Lidopel's application request a "new indication for a use"?**



[3] 138 Cong. Rec. H9099 (September 22, 1992).



In addition, Lidopel's current package insert labeling references a maximum dosage of 80 mAmin The Dosage and Administration section states in relevant part:

In the application at issue here, Empi requests a new higher dosing recommendation of 80 mAmin. We believe that this important relevant modification of dosage is a new "indication for a use" as described under 21 CFR 201.57(c). For example, 21 CFR 201.57(c)(3)(i) states in part:

> ... If the information is relevant to the recommended interval between doses, the usual duration of treatment, or *any modification of dosage*, it

> shall be stated in the "Dosage and Administration" section of the labeling and referenced in this section.
>
> (Emphasis added.)

Because the Lidopel application proposes [redacted] which is a new claim and also includes a new higher dosing recommendation, Empi's application for Lidopel is considered to have new "indications for a use." Therefore, Empi's Lidopel application meets the second condition for a human drug application submitted under section 505(b)(2) of the Act and is subject to a fee. If Empi wishes to avoid paying the user fee, Empi can revise the proposed labeling of their product to remove [redacted] indication[4] and the higher dosing recommendations.

D. Does the device status of iontophoresis affect the determination of the applicability of user fees to this application?

You state that FDA's Center for Devices and Radiological Health (CDRH) has provided varying advice on the required regulatory clearance for iontophoresis. You further assert that this alleged policy ambiguity unfairly requires an application user fee for device manufacturers who seek approval of a prescription drug for iontophoretic delivery, while other device manufacturers with a general indication, "for administration of ionic solutions" as class II devices, are not required to pay a fee. You conclude that device manufacturers are "forced" to seek NDA approvals for drugs labeled for iontophoretic delivery.

Generally, once you submit an NDA, you pay a user fee. However, it was your choice to submit an NDA rather than submit your device with the general indication "for administration of ionic solutions."

E. Does FDA's interpretation mean that all 505(b)(2) applications pay a fee?

You have asserted that FDA attempts to interpret the statute broadly so that all 505(b)(2) applications become subject to user fees. You further assert that FDA has determined that "indication for use" means "all labeling statements." As discussed above, this is not the case. Since the inception of user fees, each year there have been several 505(b)(2) applications not assessed a fee. For example, we have had applications that differ in inactive ingredients or dosage form (e.g., ready-to-use injection v. lyophilized powder) in which the 505(b)(2) labels differ from the approved labeling. However, because they did not include a new "indication for a use," these applications were not assessed fees.

III. Conclusion

We believe that the application submitted by Empi for Lidopel is considered a human drug application according to the statute. As such, an application fee is expected.

If you have further questions regarding this matter or other user fee questions, please contact Michael Jones of the Office of Regulatory Policy, at 301-594-2041 or Lynn Whipkey or Dan Troy of the Office of Chief Counsel at 301-827-7137.

Sincerely,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc:

User Fee File, HFD 5
M.Jones, HFD-5
C.Vincent, HFM-51
V.Kao, HFD-170

c:\data\firmcorr\letters\lidopel v12.doc

Drafted 5/6/2002 M.Jones
Revised 5/15/2002 M.Jones
Comments ~5/22/2002 J.Axelrad
Revised 6/19/2002 P.Varki
Revised 6/20/2002 M.Jones
Revised 6/20/2002 P.Varki
Revised 6/21/2002 M.Jones
Sent to HFD-170 for comment 6/21/2002
Edited 6/28/2002 S.O.Malley
Revised 6/28/2002 M.Jones
Revised 7/22/2002 J.Axelrad
Revised 7/23/2002 M.Jones
Comments 7/23/2002 J.Axelrad
Revised 7/24/2002 M.Jones
Edits 7/25/2002 S.O'Malley
Revised 7/26/2002 M.Jones
Comments 9/19/2002 L.Whipkey
Revised 9/19/2002 M.Jones
Comments 9/24/2002 HFD-170
Revised and Final 9/24/2002 M.Jones
Comments J.Axelrad 9/24/2002
Comments L.Whipkey 9/25/2002
Comments HFD 170 9/25/2002
Final 9/26/2002 M.Jones

MJones
9-26-2002

Memo to File 4-02-02

[The following emails document the discussions on the user fee question re N21-486 Lidopel. The Division, in consult with Mike Jones and Leah Ripper, determined that the proposed labeling specifies a new dosing regimen different from that of the referenced drug's and that user fees are applicable. Sponsor was informed 4-2-02 of the decision.]

This definitely appears to be a new dosing regimen.

Bob

-----Original Message-----
From: Jones, Michael D
Sent: Friday, March 29, 2002 10:52 AM
To: Rappaport, Bob A; McCormick, Cynthia G
Cc: Jani, Parinda; Ripper, Leah W; Kao, Victoria; Jones, Michael D; Brice, Tawni M; Friedman, Beverly J
Subject: RE: update on Lidopel 505b2 user fee issue

I have been out of the office most of this week and I have not seen a response. I thought I would chime in. In order to determine if the sponsor has to pay a fee for this 505b2 application we need to determine if they have requested a new "indication for a use" (a broader concept than indication). FDA has determined that a new "indication for a use" includes new dosing regimens.

If the 80 mAmin is considered a new dosing regime, then we would consider it a new "indication for a use" and it would be fee liable. The division needs to determine if the 80 mAmin is a new dosing regime.

It looks clear to me that this is a new dosing regime, since the approved labeling limits the dosing to 40 mAmin but I could be overlooking something. What do you folks think?

Mike

-----Original Message-----
From: Kao, Victoria
Sent: Wednesday, March 27, 2002 11:13 AM
To: Rappaport, Bob A; McCormick, Cynthia G
Cc: Jones, Michael D; Jani, Parinda; Ripper, Leah W
Subject: update on Lidopel 505b2 user fee issue

On 3/19, Mike Jones, Leah Ripper, Parinda and I sat down to discuss the user fee issues surrounding the N21-486 Lidopel (lidocaine and epinephrine) application. The Sponsor had submitted it as a no fee 505 b2, claiming that Lidopel references an approved drug product (Iontocaine) with the same molecular entity and indication for use.

We took issue because there seems to be a new dosing regime proposed in the current Lidopel product that's different from approved Iontocaine's:

Approved Iontocaine labeling says: "Due to lack of clinical experience, administration of doses greater than 40mAmin is not recommended."

Whereas the current proposed label says "

ndicate that a 80mAmin dose is safe and effective.

We expect that if the approved Iontocaine tried to make such a dosage change, we'd request a supplement with clinical data and the proper fee. So it seems logical to request fees from a b2 applicant coming in for these same changes.

After our 3/19 meeting, our position remains the same.

The Sponsor's argument, faxed in on March 13, basically says:

1) If extrinsic factors (such as thickness, degree of hydration of skin) were controlled, the Iomed device used with the approved Iontocaine would deliver the same amount of drug as the current Lidopel device if they are operated at the same mAmin. So, same mAmin, same amt of drug delivered.

2) The total amount of lidocaine/epinephrine delivered by any iontophoretic device, at either 40mAmin or 80 mAmin is extremely small and will be well below the maximum dose recommended in the labeling for other approved lidocaine/epinephrine products.

3) The actual dose administered to a patient in ordinary clinical use is determined by the physician. That dose, whatever it may be, will be similarly chosen, whether the current device, or any other iontophoretic device is used.

These arguments seemed weak to us. We are seeking concurrence from the medical perspective.

Thanks, Vicki

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

/s/

Victoria Kao
4/3/02 12:57:34 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

2/28/02

NDA 21-486

Kirkpatric & Lockhart, LLP
1800 Massachusetts Ave., N.W.
Washington DC 20036
Attention: Gary L. Yingling, Esq.

Dear Mr. Yingling:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lidopel® (2% lidocaine HCl and epinephrine 1:100,000) on behalf of Empi, Inc.

Date of Application: February 8, 2002

Date of Receipt: February 11, 2002

Our Reference Number: NDA 21-486

We have not received the appropriate user fee for this application. An application is considered incomplete and can not be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by courier should be delivered to:

Food and Drug Administration (360909)
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.

The receipt date for this submission (which begins the review for fileability) will be the date the review division is notified that payment was received by the bank.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care,
and Addiction Drug Products, HFD-170
Attention: Division Document Room, 9B-23
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Victoria Kao, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Acting Chief, Project Management Staff
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Parinda Jani
2/28/02 08:46:23 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004

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

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

2. TELEPHONE NUMBER *(Include Area Code)*

(651) 415-9000

3. PRODUCT NAME Lidopel™ Lidocaine HCl 2% and Epinephrine 1:100,000

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
■ YES ☐ 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:

■ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

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

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

■ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ 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.)

☐ 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.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(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

and

Food and Drug Administration
CDER, HFD-94
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	DATE
H. Philip Vierling	President & Chief Operating Officer	2/4/2002

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-2454 EF

19. FINANCIAL INFORMATION

In compliance with 21 CFR 54, the required Certification of Financial Interests and Arrangements of Clinical Investigators (FDA Form 3454) is provided in APPENDIX 19-1. Certification requirements do not apply to Studies #96-08.0 and #97-07.0 since they were completed prior to February 2, 1998, the effectiveness date of this requirement.

APPENDIX 19-1

Financial Certification Form
(and Attachment)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

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 Attachment	

☐ (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	TITLE
H. Philip Vierling	President & Chief Operating Officer
FIRM/ORGANIZATION: Empi, Inc.	
SIGNATURE: H Phil Vierling	DATE: 2/4/2002

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

FORM FDA 3454 (3/99)

Created by Electronic Document Services/USDHHS: (301) 443-2454

Attachment to FDA Form 3454
Certification: Financial Interests and Arrangements of Clinical Investigators

As specified in FDA Form 3454, Item 1:

The following Investigators did not participate in any financial arrangement with Empi, Inc., whereby the value of compensation to the investigator could be affected by the outcome of the studies as defined in 21 CFR 54.2(a). Each listed investigator did not disclose any proprietary interests in the product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b). Furthermore, no listed investigator was the recipient of significant payments of the sorts defined in 21 CFR 54.2(f).

Investigators	Clinical Site	Study
		#99-02.0
		#99-07.0 #00-1-03.0 #01-1-06.0

Pre-NDA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 54, 731

Empi, Inc.
C/o Kirkpatrick and Lockhart, LLP
1800 Massachusetts Ave., N.W. 2nd Floor
Washington, D.C., 20036-1221

Attention: Gary L. Yingling, Esq.
Regulatory Counsel

Dear Mr. Yingling:

Please refer to the pre-NDA meeting between representatives of your firm, Empi, Inc. and FDA on July 20, 2001. The purpose of the meeting was to discuss the impending submission of your 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: July 20, 2001 **Time:** 12:00 noon EST
Location: Parklawn Conference Center, Rm L.
Sponsor: Empi, Inc.
IND: 54,731
Drug: 2% Lidocaine and Epinepherine 1:100,000 via the Dupel® Iontophoresis System
Indication: ———
Meeting Chair: Bob Rappaport, M.D.
Minutes Recorder: Kimberly Compton, Regulatory Project Manager

FDA Attendees:	Titles:	Offices:
Cynthia McCormick, M.D.	Director	HFD-170
Bob Rappaport, M.D.	Deputy Division Director	HFD-170
Harold Blatt, D.D.S.	Clinical Reviewer	HFD-170
Suzanne Thornton, Ph.D.	Pharmacology/Toxicology Reviewer	HFD-170
Thomas Papoian, Ph.D.	Supervisory Pharmacologist	HFD-170
Dale Koble, Ph.D.	Chemistry Team Leader	HFD-170
Eric Duffy, Ph.D.	Division Director, ONDC II	HFD-820
Stella Grosser, Ph.D.	Biostatistician	HFD-170
Suresh Doddapaneni, Ph.D.	Biopharmaceutics Team Leader	HFD-170
George Liao	Regulatory Health Information Specialist	HFD-170
Kimberly Compton	Regulatory Project Manager	HFD-170

Participants:	Titles:
Philip Vierling	Empi, President and COO
Paul Ricciatti	Novocol, Vice President of Operations
	Statistician Consultant
Gary Yingling	Regulatory Counsel
Rebecca Dandeker	Regulatory Counsel

Meeting Objective: To answer the questions posed by the sponsor in order to provide guidance regarding the anticipated submission of the NDA for this drug product/device combination.

General Discussion: The sponsor opened the meeting by giving a brief overview of the product and anticipated application. They stated that they would be seeking to have their drug labeled only for use with the Dupel device. The Dupel device is now generally labeled for use with other appropriate drugs. The sponsor intends the drug to be labeled as '

Septodent will manufacture the product for Empi.

Dr. Rappaport stated that the overall development plan appeared to be adequate and that there were probably no major concerns, but without having the electrode label in the package we are unable to fully assess the sponsor's proposed plan to evaluate dosing and administration. He went on to say that the Agency may need more information on this issue and that it would be discussed at today's meeting.

1. *Empi expects that the data to be submitted in the 505(b)(2) NDA, as outlined in the Pre-NDA Briefing Document, is sufficient to obtain a label indication for Empi's, 2% Lidocaine HCl and Epinephrine 1:100,000*

Response:
Comments on Human Dosing Study
Skin Irritation from Repeated Doses (Same Site)

- Repeated dose should be tested immediately, not 7 days later.
- If first dose fails, next dose may be immediately administered at same site.
- Immediate subsequent dosing may cause skin irritation.

Comments on Trials

- Appears Adequate and Well-controlled
- Number of Subjects: potentially too small?
  - Exposed: 4 mA for 20 minutes: 51 Subjects
  - Exposed: 4 mA for 15 minutes: 35 Subjects

Dr. Rappaport stated that other procedures than those studied could be envisioned and these may require repeat dosing rather quickly. Data on such dosing is needed. He went on to say that the numbers of patients with repeat dosing did not need to be very large. Dr. McCormick inquired if the sponsor has measured the duration The sponsor replied that they have results of about 30 minutes duration of analgesia, which was adequate for the procedures studied. The sponsor inquired how many repeat doses they would need to study. Dr. Rappaport stated that one might be enough if

Dr. Rappaport stated that the Agency is unclear regarding the number of subjects, population, dose being studied, etc. The sponsor stated that the dose is intended for use with venipuncture and that up to may be used for shaves. Dr. Rappaport stated that since

the majority of patients will be treated at the lower dose and there is some exposure at higher doses, the numbers of subjects may be acceptable.

2. *For the CMC section of the NDA, Empi plans to include the following: (1) the FDA cleared 510(k) for the iontophoresis device, (2) a brief summary of and reference to ANDA 84-048 regarding the drug product which is to be relabeled as Empi's 2%, Lidocaine HCl and Epinephrine 1:100,000 for administration via iontophoresis, and 3) a letter from Septodont, originator of ANDA 84-048, authorizing Empi to reference the data in this ANDA. Does the Agency agree that this information is sufficient for a CMC section to support approval of Empi's NDA?*

   Response:
   No. The CMC portion of the NDA needs to be complete either by submission of the information in the NDA, or by reference to other applications submitted to FDA. [The following is a preliminary list of information to be included in the NDA (see appropriate FDA guidelines.)]

   (a) For the ANDA drug product provide the following in the NDA (if possible) and a specific reference (submission date, volume number, page number) to the ANDA:
   - Drug substance specifications
   - Drug product specifications
   - Expiration dating period for the drug product
   - Current sites (and CFN #s) of drug substance/drug product manufacturing and testing (for inspection)

   (b) Provide specifications for impurities in the ANDA drug substance and drug product in accordance with ICH [update to the ANDA may be necessary].

   (c) Provide acceptance specifications to be used by EMPI for the ANDA drug product, a description of the protocol that will be used to label the product with the correct expiration date, etc.

   (d) Provide the name, address, and CFN# for the facility to be used by EMPI for labeling the drug product obtained from the ANDA holder.

   (e) Provide detailed identification of the investigational formulations, ionotophoretic devices, and electrodes used in the clinical trials; including certificates of analysis for the ANDA drug product, device/electrode production numbers, clinical protocol numbers, etc. Any differences between the ANDA product or the 510(k) products studied in the clinical investigations and the to-be-marketed products should be indicated and justifications/data provided to support the suitability of the changes in terms of drug product performance. [This information cannot be referenced anywhere else and is a very important section of the application.]

(f) Provide studies demonstrating acceptable drug delivery for the drug product at the extremes of the ANDA drug product specifications (e.g., pH).

(g) Provide a specification for [redacted] and a regular schedule for testing of this attribute.

(h) Provide a description of how changes in the ANDA drug product or the iontophoretic device/electrode will be controlled, documented, and reported to the Agency (e.g., the letter of authorization from the ANDA holder should include a suitable commitment concerning changes in the ANDA).

The sponsor stated that the information stated in (a) could be provided and that the ANDA was approved in approximately 1980 and that there is only one supplier of the drug product and substance to the sponsor. Dr. Koble reminded the sponsor that this application will need to meet current standards regarding impurities, ICH guidelines, etc.

Regarding point (g), [redacted]

Regarding point (h), Dr. Koble stated that any changes to the ANDA would need to be communicated to our Division. The sponsor stated that they could create a protocol to accommodate this need. Dr. McCormick reminded the sponsor that regarding any future changes, safety is always of paramount concern.

3. *Does the Agency agree that the statistical analyses of the clinical studies conducted under IND 54,731, which were conducted using SPSS, is acceptable?*

   Response:
   SPSS is acceptable. Statistical analyses will be reviewed with the NDA.

Dr. Grosser stated that SAS format is preferable and the sponsor responded that they could transfer the data into SAS.

4. *Does the Agency agree that it is acceptable for Empi to provide the NDA information in paper form, with the exception that the clinical data will be provided in electronic form?*

Response:
Submissions in electronic format are highly preferred and encouraged, to facilitate the review process.

Important Highlights:
"Providing Regulatory Submissions in Electronic Format" [guidance on the web].

- Data set size should be < 25MB/file - if not, Divide into smaller datasets.
- Each Subject should have a Single Unique Marker for the Whole Application.
- All Date variables should use the same format.
- Time, Start and Stop times, and Dates should be
  - based on start of study treatment
  - show duration of treatment
  - be expressed in minutes, hours, or days as appropriate
- Each dataset should include
  - study, center, treatment assignment
  - sex, age, and race
  - Text should be used for these variables in addition to codes. [both text and codes should be used].

5. *Does the Agency agree that Empi need not submit individual case report forms since the studies involved no patient deaths and no serious adverse events and, as contemplated in 21 C.F.R. § 314.50(f)(2), the case report forms are unnecessary for a proper review of the study and study data?*

   Response:
   Regulations specify the need to provide the CRFs for subjects who discontinued due to an AE. We reserve the right to request any and all CRFs during the review process.

6. *Does the Agency agree that Empi's stability data appear to support the stability of the product for purposes of approving the NDA?*

   Response:
   Presumably this refers to the stability under iontophoretic conditions. A detailed evaluation during NDA review will be necessary before the acceptability of the compatibility is determined.

   Provide a detailed description of the studies (including description and validation of the analytical methods, etc.) performed to generate the compatibility and stability of the drug product under iontophoretic conditions.

Dr. Koble referred the sponsor to detailed CMC comments sent to the sponsor early in the IND review process.

The sponsor would prefer to submit the NDA now and address the multiple-dose information later in a supplement. If the Division agrees, the sponsor can submit the NDA within 3-4 weeks, after they have responded to the Division's questions, and gathered other required information. Dr. McCormick agreed that this was acceptable to the Division.

Action Items:

- The Agency will provide the sponsor with a copy of the official meeting minutes.

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
8/20/01 03:14:48 PM

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FDA-INDUSTRY END-OF-PHASE II MEETING MINUTES

Meeting Date: June 30, 1999 **Time:** 2:30-4:00 PM

Location: Parklawn Building, Potomac Conference Room

IND Name: 54,731, 2% Lidocaine HCl and Epinephrine 1:100,000 via Dupel Iontophoresis System

Sponsor: Empi, Inc.

Type of Meeting: End-of-Phase II Meeting

Meeting Chair: Cynthia McCormick, M.D.

Minutes Recorder: Susmita Samanta/ Project Manager

FDA Attendees:	Titles:	Offices:
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Bob Rappaport, M.D.	Deputy Division Director	HFD-170
Hal Blatt, D.D.S.	Medical Reviewer/Anesthetic	HFD 170
Albinus D'Sa, Ph.D.	Team Leader/Chemistry	HFD-820
Pat Maturu, Ph.D.	Chemistry Reviewer	HFD-820
Dou Huey Jean, Ph.D.	Team Leader/Pharmacology	HFD-170
Tom Permutt, Ph.D.	Team Leader/Biostatistician	HFD-170
Corinne P. Moody	Chief, Project Management Staff	HFD-170
Susmita Samanta	Project Manager	HFD-170
Suresh Doddapaneni, Ph.D.	Bio-Pharm Reviewer	HFD-870
Z.Jonathan Ma, Ph.D.	Biostatistician	HFD-170
John Gibbs, Ph.D.	Supervisor/Chemistry	HFD-820
Patricia Hartwell, M.D.	Medical Reviewer	HFD-170
Henry Startzman, M.D.	Medical Reviewer	HFD-170
Donald Hare	Special Assistant to the Director/OGD	HFD-604

Sponsor Attendees:	Titles:
Deborah Jensen	VP of RA, QA and Clinical Research
Lisa Wipperman Heine, M.S.	Director, Clinical Research and RA
Carolyn Steele Husten, M.M.S.E., RAC	Regulatory Affairs Manager
Jill Cernohous, M.A.	Manager, Clinical Research
—	Medical Monitor
Richard Holcomb, Ph.D.	Statistician
—	Regulatory Consultant

Meeting Objective:
The primary objective of this meeting was to confirm the acceptability of submitting a New Drug Application (NDA) for 2% lidocaine HCl and epinephrine 1:100,000 administered via the Dupel Iontophoresis System and confirm the acceptability of two Phase III studies.

Background:
The sponsor requested an End-of-Phase II meeting for the IND 54, 731 on May 5, 1999, received by the Agency on May 6, 1999. A letter confirming the date and time of the meeting was issued on May 19, 1999. The meeting package was received on June 1, 1999. The meeting package contained five questions for the Agency.

Specific questions and responses:

1) Confirm the acceptability of submitting a NDA for 2% lidocaine HCL and epinephrine 1:100,000 via Dupel Iontophoresis System as a [redacted] under 505 (b) (2), relying in part on published literature and data submitted in NDA 20-530 regarding the iontophoretic delivery of 2% lidocaine HCL and epinephrine 1:100,000.

Dr. McCormick led the discussion and informed the sponsor of the following:

- The Agency needs to know in what aspects this product differ form the listed product (drug/device combination). If there are specific aspects of the device that are substantially different (chemistry, electrodes, electrical current), the differences should be identified. In that case, clinical studies of safety or efficacy, or both would be necessary.
- If there are no identifiable differences, a therapeutic equivalence trial might be needed.
- The sponsor needs to provide data to substantiate the claim that this is a 505(b)2 application.
- [redacted]

2) Does the Agency agree that the inclusion of approximately 200 combined subjects from the completed and proposed studies in Empi's clinical plan is adequate to support the safety and efficacy of the iontophoretic administration of 2% lidocaine HCl and Epinephrine 1:1000,000 [redacted] given the related published literature and approval of NDA 20-530?

Dr. McCormick responded that it will depend on how this product differs from the existing product. If there are significant differences that raise specific safety concerns, then a database of approximately 300 patients would be more appropriate. If there are no appreciable differences, then the requirements under Generic regulations would apply.

Dr. Jonathan Ma (Biostatistics Reviewer) responded:

- Uneven sample sizes may be considered to increase patient exposure to the active treatment.

3) Confirm the acceptability of the study design for the Phase 3 study #99-02.0, "Anesthetic Effect of 2% Lidocaine HCL and Epinephrine 1:100,000 Delivered via the Dupel Iontophoresis System to Subjects Undergoing Shave Removals".

Dr. Jonathan Ma responded :

- It is not clear from the protocol how the optimum effective dose will be determined in the Part I of Study 99-02.0 and whether that minimum effective dose would be the optimal dose level the sponsor would eventually market. In fact, a dose level that differs statistically significantly from the placebo is not necessarily the one that provides the most clinically satisfactory outcomes.

- The definition of treatment failure also contains subjects who cannot tolerate the iontophoretic procedure. These subjects are different from those who failed due to inadequate anesthesia and it would be desirable to examine how they distribute across treatment groups.

a) Does the Agency agree that the end points are adequate to achieve the stated objectives?

Dr. McCormick responded that pain rating should be a primary instead of a secondary endpoint. Minimum effective dose is usually determined in Phase I or II.

b) Does the Agency agree that the comparison of placebo treatment versus active treatment is acceptable?

Dr. McCormick responded that it is adequate but the sponsor should consider 3rd arm with existing listed iontophoretic product to demonstrate therapeutic equivalence.

4) Confirm the acceptability of the study design for the Phase 3 study #99-07.0, "Phase 3 study on Anesthetic Effect of 2% Lidocaine HCL and Epinephrine 1:100,000 delivered via the Dupel Iontophoresis System to Subjects Undergoing Venipuncture".

Dr. McCormick responded that it was acceptable.

a) Does the Agency agree that the end points are adequate to achieve the stated

objectives?

Dr. Ma responded that the protocol gives conflicting statements about what is the primary efficacy endpoint. Page 9 says pain score (VAS 1-100), but Page 27 says satisfaction ratings (1-10).

b) Does the Agency agree that conducting the study using normals and within subject placebo controls is adequate?

Dr. McCormick responded that they appear to be adequate.

5) Does the Agency agree that the proposed package insert for 2% lidocaine HCL and epinephrine is acceptable?

Dr. McCormick responded that it is premature to comment on the labeling at this point.

Conclusion:

The meeting concluded with the agreement that the sponsor will be providing the Agency with a package defining differences between the proposed application and the existing application. The Agency on the other hand will

Minutes Prepared By: S.Samanta Susan Samanta

Minutes Concurred By Chair: Cynthia G. McCormick, M.D. Cynthia M McCormick MD