

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022396Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

Dyloject™ (diclofenac sodium) Injection, 37.5 mg/mL Module 1: Administrative Information NDA 22-396	1.3 Administrative Information 1.3.5.1 Patent Information Page 1 of 4
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**Patent and Exclusivity**

**TIME SENSITIVE PATENT INFORMATION**

Pursuant to 21 CFR 314.53  
For  
NDA 22-396

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: Dyloject™  
Active Ingredient: Diclofenac sodium  
Strength: 37.5 mg/mL  
Dosage Form: 37.5 mg/1 mL (b)(4) single-use vials

A. This section should be completed for each individual patent

**U.S. Patent Number:** 5,679,660

**Expiration Date:** December 2, 2014

**Type of Patent- Indicate all that apply**

- |   |   |  |
|---|---|--|
| 1. Drug Substance (Active Ingredient)     | yes <input type="checkbox"/>            | no <input checked="" type="checkbox"/> |
| 2. Drug Product (Composition/Formulation) | yes <input checked="" type="checkbox"/> | no <input type="checkbox"/>            |
| 3. Method of Use                          | yes <input type="checkbox"/>            | no <input checked="" type="checkbox"/> |

If patent claims method(s) of use, please specify approved method(s) of use for which approval is being sought that are covered by patent: not applicable

**Name of Patent Holder:** Farnarc Nederland BV

U.S Agent: (if patent holder does not reside or have a place of business in the US):

Javelin Pharmaceuticals, Inc.  
125 CambridgePark Drive  
Cambridge, MA 02140

Dyloject™ (diclofenac sodium) Injection, 37.5 mg/mL Module 1: Administrative Information	1.3 Administrative Information 1.3.5.1 Patent Information
NDA 22-396	Page 2 of 4

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use Claims.

The undersigned declares that the above stated United States Patent number 5,679,660 covers the formulation of Dyloject™ Injection. The product is:

\_\_\_\_\_ currently approved under section 505 of the Federal Food, Drug and Cosmetic Act.

OR

the subject of this application for which approval is being sought.

---

Signed:

Roberta Tucker

Date:

Sept. 14, 2009

Title:

Acting VP Regulatory Affairs

Telephone Number:

508 842 9339

Dyloject™ (diclofenac sodium) Injection, 37.5 mg/mL Module 1: Administrative Information	1.3 Administrative Information 1.3.5.1 Patent Information
NDA 22-396	Page 3 of 4

**TIME SENSITIVE PATENT INFORMATION**

Pursuant to 21 CFR 314.53  
For  
NDA 22-396

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: Dyloject™  
Active Ingredient: Diclofenac sodium  
Strength: 37.5 mg/mL  
Dosage Form: 37.5 mg/1 mL (b)(4) single-use vials

B. This section should be completed for each individual patent

**U.S. Patent Number:** 6,407,079

**Expiration Date:** June 18, 2019

**Type of Patent- Indicate all that apply**

- 1. Drug Substance (Active Ingredient)                    yes  no X
- 2. Drug Product (Composition/Formulation)            yes X no
- 3. Method of Use    yes  no X

If patent claims method(s) of use, please specify approved method(s) of use for which approval is being sought that are covered by patent: not applicable

**Name of Patent Holder:** Janssen Pharmaceutica N.V.

U.S Agent: (if patent holder does not reside or have a place of business in the US):

Janssen Pharmaceutica, Inc.  
125 Trenton Harbourton Road  
Titusville, NJ 08560

Dyloject™ (diclofenac sodium) Injection, 37.5 mg/mL Module 1: Administrative Information	1.3 Administrative Information 1.3.5.1 Patent Information
NDA 22-396	Page 4 of 4

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use Claims.

The undersigned declares that the stated United States Patent number 6,407,079 covers the formulation of Dyloject™ Injection. The product is:

\_\_\_\_\_ currently approved under section 505 of the Federal Food, Drug and Cosmetic Act.

OR

✓ the subject of this application for which approval is being sought.

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Signed:

Roberta Tucker

Date:

September 14, 2009

Title:

Acting VP Regulatory Affairs

Telephone Number:

508 842 9339

## EXCLUSIVITY SUMMARY

NDA # 022396

SUPPL # NA

HFD # 170

Trade Name Dyloject (diclofenac sodium) Injection 37.5 mg/mL

Generic Name diclofenac sodium

Applicant Name Javelin Pharmaceuticals, Inc.

Approval Date, If Known 23 December 2014

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505 (b)(2)

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

YES  NO

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

NA

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

NA

d) Did the applicant request exclusivity?

YES  NO

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

3 years

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

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

NA

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES  NO

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

NDA #	204592	Zorvolex (diclofenac) Capsules 18 mg, 35 mg
NDA#	021234	Flector (diclofenac epolamine) Patch, 1.3%
NDA#	022202	Zipsor (diclofenac potassium) Capsule 25 mg
NDA#	022165	Cambia (diclofenac potassium) For Solution, 50 mg
NDA#	020142	Cataflam (diclofenac potassium) Tablets, 50 mg
NDA#	021005	Solareze (diclofenac sodium) Gel 3%
NDA#	022122	Voltaren (diclofenac sodium) Gel 1%
NDA#	020037	Voltaren (diclofenac sodium) Ophthalmic Solution/Drops 0.1%
NDA #	020947	Pennsaid (diclofenac sodium) 1.5% Topical Solution
NDA #	204623	Pennsaid (diclofenac sodium) 2% Topical Solution
NDA #	020254	Voltaren-XR (diclofenac sodium) Extended Release Tablets, 100 mg
NDA#	20607	Arthrotec (diclofenac sodium) Delayed Release Tablets, 50 mg/0.2 mg; 75 mg/0.2 mg

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES," GO TO PART III.

### **PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

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

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

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

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

NA

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

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

NA

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

YES  NO

If yes, explain:

NA

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

DFC-004- A Randomized, Double-Blind, Active- and Placebo-Controlled Study of the Analgesic Efficacy and Safety of Repeated Dosing of Two Dose Levels of DIC075V Relative to Parenteral Ketorolac and Placebo in Patients with Acute Postoperative Pain after Abdominal or Pelvic Surgery

DFC-005 - A Randomized, Double-Blind, Active- and Placebo-Controlled Study of the Analgesic Efficacy and Safety of Repeated Dosing of DIC075V Relative to Parenteral Ketorolac tromethamine and Placebo in Patients with Acute Post-Operative Pain after Elective Orthopedic Surgery

DFC-010 - An Open-Label, Multiple-Dose, Multiple-Day, Nonrandomized, Single-Arm Safety Study of Repeat-Doses of Dic075v (Intravenous Diclofenac Sodium) in Patients with Acute Post-Operative Pain

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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

NA

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

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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

NA

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application

or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

DFC-004  
DFC-005  
DFC-010

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

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

Investigation #1  
IND # 65048      YES       ! NO   
! Explain:

Investigation #2  
IND # 65048      YES       ! NO   
! Explain:

Investigation #3  
IND # 65048      YES       ! NO   
! Explain:

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

NA

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

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

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

YES  NO

If yes, explain:

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Name of person completing form: Swati Patwardhan  
Title: Regulatory Project Manager, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)  
Date: Dec 23, 2014

Name of Office/Division Director signing form: Rigoberto A. Roca  
Title: Deputy Director, DAAAP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

SWATI A PATWARDHAN  
12/23/2014

RIGOBERTO A ROCA  
12/23/2014

<b>Dyloject™ (diclofenac sodium) Injection, 37.5 mg/mL</b>	<b>1.3 Administrative Information</b>
<b>Module 1: Administrative Information</b>	<b>1.3.3 Debarment Certification</b>
<b>NDA 22-396</b>	<b>Page 1 of 1</b>

### Debarment Certification

In accordance with Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, Javelin Pharmaceuticals, Inc. hereby certifies that, in connection with this application, it did not and will not use in any capacity the services of any debarred person.

*Roberta Tucker*

Roberta Tucker  
Acting Vice President  
Regulatory Affairs  
Javelin Pharmaceuticals, Inc.

*Sept. 14, 2009*

Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 022396 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Dyloject Established/Proper Name: diclofenac sodium Dosage Form: Injection solution		Applicant: Javelin Pharmaceuticals, Inc. (c/o Hospira, Inc.) Agent for Applicant (if applicable):
RPM: Swati Patwardhan		Division: Div. of Anesthesia, Analgesia, and Addiction Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="text-align: center;"><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p style="margin-left: 20px;"> <input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check: Dec.22, 2014         </p> <p style="margin-left: 20px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>December 31, 2014</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input type="checkbox"/> None CR: Dec 23, 2013 CR: Oct 1, 2010
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): Type-3 New Dosage form  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) AP: 12/22/14 CR: 12/23/13 CR: 10/1/10
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	Granted: 10/11/13, 3/22/10 Reviews: 10/11/13 7/29/10 3/29/10
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	
• Review(s) <i>(indicate date(s))</i>	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> None DMEPA: <input type="checkbox"/> None 9/1010, 11/8/13 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input type="checkbox"/> None 12/10/3, 12/17/14 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 10/13/10 11/27/13, 12/9/14
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
○ If yes, Center Director's Exception for Review memo ( <i>indicate date</i> )	
○ If yes, OC clearance for approval ( <i>indicate date of clearance communication</i> )	<input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> )	
• Date reviewed by PeRC <u>Nov 6, 2013</u> If PeRC review not necessary, explain: _____	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	√
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	√
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 3/10/08
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 4/21/06
• Mid-cycle Communication ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A
• Late-cycle Meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/1/10, 12/23/13, 12/23/14
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/11/13, 12/22/14
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )	9/3/10,
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Page 17 of clinical review dated 9/3/10

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None DCRP/ 4/19/10
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 8/10/10, 9/13/10, 11/28/11, 11/30/11
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8/10/2010
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8/17/10
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 8/19/10
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8/30/2010, 12/12/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 9/30/10, 12/4/13, 12/19/13, 12/19/14
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 9/2/2010, 9/24/2010, 10/1/2010,
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 8/2/10
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<input checked="" type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	9/13/10
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: 12/18/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/  
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PARINDA JANI  
01/05/2015

## Patwardhan, Swati

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**From:** Patwardhan, Swati  
**Sent:** Monday, December 22, 2014 6:08 AM  
**To:** Townsend, Steven E. (Steven.Townsend@hospira.com)  
**Subject:** Re: NDA 022396 Draft labeling  
**Attachments:** NDA 022396 draft labeling to Sponsor 122214.doc

**Importance:** High

Hi Steven,  
Please find attached the draft labeling with our changes proposed in track format. Please accept any changes with which you concur, and then make any revisions you deem necessary. Please also submit a clean word file.

Since there were revisions made, we may have missed typos, cross references, etc., and some of the heading formatting might be off. Please send the revised version by noon tomorrow December 23, 2014 via email to me. Please do not submit the draft labeling as an amendment to the NDA.

Let me know if there are any questions.

Thank you

Swati Patwardhan  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)  
Center of New Drug Evaluation and Research  
Phone: 301-796-4085  
Fax: 301-796-9748

17 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS)  
immediately following this page

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/s/  
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SWATI A PATWARDHAN  
12/22/2014



# Memorandum

Date: December 18, 2014

From: Juandria Williams, Ph.D.  
Compliance Officer  
New Drug Manufacturing Assessment Branch  
Division of Good Manufacturing Practice Assessment  
Office of Manufacturing and Product Quality

Subject: (b) (4) Response Review Memo for NDA 22396, Diclofenac Sodium Injection, 37.5 mg/mL

Thru: Mahesh Ramanadham, Branch Chief, NDMAB, OMPQ/DGMPA

To: Julia Pinto, Acting Branch Chief, Branch VIII, ONDQA/Division III

Applicant: Javelin Pharmaceuticals  
275 North Field Dr.  
Department 0392, Building H2-2  
Lake Forest, IL 60045

Establishment: (b) (4)

The Division of Good Manufacturing Practice Assessment (DGMPA) has completed a review of (b) (4) follow-up response to an observation cited on the FDA Form 483 issued October 22, 2013 upon the completion of a pre-approval inspection for NDA 22396. The application was withheld, in part, due to the firm's inadequate initial response to the observation:

(b) (4)

(b) (4)

NDA 22396 (Diclofenac Sodium Injection, 37.5 mg/mL)

(b) (4)

If you have any questions, please contact me at (301) 796-4196 or by email at [juandria.williams@fda.hhs.gov](mailto:juandria.williams@fda.hhs.gov).

Juandria Williams, Ph.D.  
Compliance Officer  
OC/OMPQ/DGPMA/NDMAB

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/s/  
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JUANDRIA WILLIAMS  
12/19/2014

MAHESH R RAMANADHAM  
12/19/2014

## Patwardhan, Swati

---

**From:** Kapoor, Rachna  
**Sent:** Thursday, December 19, 2013 10:12 AM  
**To:** Patwardhan, Swati; Walker, Morgan  
**Subject:** RE: Carton and container labels for Dyloject - NDA 022396

Hi Swati,

I just checked the labels with the review. The carton and container labels for Dyloject are acceptable.

Thanks

Rachna

Rachna Kapoor, Pharm.D.  
Safety Evaluator  
Division of Medication Error Prevention and Analysis  
FDA/CDER/OSE/OMEPRM/DMEPA  
Phone: (240) 402-0217  
Fax: (301) 796-9865  
[Rachna.Kapoor@fda.hhs.gov](mailto:Rachna.Kapoor@fda.hhs.gov)

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

**From:** Patwardhan, Swati  
**Sent:** Thursday, December 19, 2013 9:35 AM  
**To:** Walker, Morgan; Kapoor, Rachna  
**Subject:** RE: Carton and container labels for Dyloject - NDA 022396

Hi Rachna and Morgan,  
Can you please confirm if the submitted carton and container labels incorporating our comments for Dyloject are acceptable

Thank you

Swati Patwardhan  
Phone: 301-796-4085

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

**From:** Patwardhan, Swati  
**Sent:** Wednesday, December 18, 2013 10:28 AM  
**To:** Walker, Morgan; Kapoor, Rachna; Peri, Prasad; Pinto, Julia; Galati, Steven; Lloyd, Joshua  
**Subject:** Carton and container labels for Dyloject - NDA 022396

Greetings!

Please find below the revised carton and container labels from Hospira for their Dyloject Product incorporating our revisions.

EDR Location: <\\CDSESUB1\evsprod\NDA022396\0044>

Julia/Prasad,

Just want to clarify that the you had proposed [REDACTED] (b) (4) but during our first review cycle we asked them to remove it as per the complete response letter from 1st review cycle. Therefore, the Sponsor was not asked to reinsert it.

Let me know if you have any additional comments. Your response either way would be appreciated by COB today.

Thank you

Swati Patwardhan  
Phone: 301-796-4085

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

From: [asr-dontreply@fda.hhs.gov](mailto:asr-dontreply@fda.hhs.gov) [<mailto:asr-dontreply@fda.hhs.gov>]

Sent: Tuesday, December 17, 2013 1:01 PM

To: CDER-EDROIM; CDER-EDR\_ASR\_Document\_Coordinators; CDER-EDRSTAFF; CDER-EDRADMIN; CDER ESUB; CDER-EDROIM; CDER-OND-DAAAP-EDRNOTIFY; Patwardhan, Swati

Subject: Successfully Processed ECTD: NDA022396 in DARRTS.

Successfully Processed ECTD: NDA022396 in DARRTS. Details below:

EDR Location: <\\CDSESUB1\evsprod\NDA022396\022396.enx>

For Document Room Staff Use:

DTD Version: 2.01

Application Type/Number: NDA022396

Incoming Document Category/Sub Category: Electronic\_Gateway

Supporting Document Number: 45

eCTD Sequence Number: 0044

Letter Date: 12/17/2013

Stamp Date: 12/17/2013

Receipt Date/Time from Notification: 12/17/2013 1:00:26 PM

Origination Date/Time from Notification: 12/17/2013 12:56:03 PM

DOCUMENT ID: 5432583

Cover Letter: <\\CDSESUB1\evsprod\NDA022396\0044\m1\us\cover-2013-12-17.pdf>

356H Form: <\\CDSESUB1\evsprod\NDA022396\0044\m1\us\356h-2013-12-17.pdf>

2252 Form: NOT FOUND

3397 Form: NOT FOUND

3674 Form: NOT FOUND

For EDR Staff Use:

The submission has already been processed. The following information is provided if verification is required. No additional action is required on your part

EDR Location: [\\CDSESUB1\evsprod\NDA022396\0044](#)

Submission Size: 1847456

Gateway Location: [\\CHDC9681\CDERESUB\inbound\ECTD\ci1387302928695.579974@fdsul08620 te2](#)

CoreID: [ci1387302928695.579974@fdsul08620 te2](#)

Copy to EDR Status: Good-1. Files were copied successfully.

For CDER Project Manager Use:

The following submission received through the Electronic Submission Gateway has been processed using the following information. This information will be updated once Document Room personnel have been able to verify the content of the submission.

Application Type/Number: NDA022396

Incoming Document Category/Sub Category: Electronic\_Gateway

Supporting Document Number: 45

eCTD Sequence Number: 0044

Letter Date: 12/17/2013

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/s/  
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SWATI A PATWARDHAN  
12/11/2014



NDA 022396

**ACKNOWLEDGE –  
CLASS 2 RESUBMISSION**

Javelin Pharmaceuticals, Inc.  
c/o Hospira, Inc.  
275 North Field Dr.  
Dept. 0392, Bldg. H2-2  
Lake Forest, IL 60045

Attention: Steven Townsend  
Associate Director, Global Regulatory Affairs

Dear Mr. Townsend:

We acknowledge receipt on October 31, 2014, of your October 31, 2014, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Dyloject (diclofenac sodium) Injection 37.5 mg/mL.

We consider this a complete, class 2 response to our December 23, 2013, action letter. Therefore, the user fee goal date is April 30, 2015.

If you have any questions, call me at (301) 796-4085.

Sincerely,

*{See appended electronic signature page}*

Swati Patwardhan  
Regulatory Project Manager  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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SWATI A PATWARDHAN  
11/14/2014



# Memorandum

Date December 17, 2013

From Juandria Williams, Ph.D.  
Compliance Officer  
New Drug Manufacturing Assessment Branch  
Division of Good Manufacturing Practice Assessment  
Office of Manufacturing and Product Quality

Subject Concurrence with (b) (4) District Office's (b) (4)-DO Withhold Recommendation for NDA 22396, Diclofenac Sodium Injection, 37.5 mg/mL.

Thru Mahesh Ramanadham, Branch Chief (Acting), NDMAB, OMPQ/DGMPA

To Prasad Peri, Branch Chief, Branch V, ONDQA/Division II

Applicant: Javelin Pharmaceuticals  
275 North Field Dr.  
Department 0392, Building H2-2  
Lake Forest, IL 60045

Establishment: (b) (4)

The Division of Good Manufacturing Practice Assessment (DGMPA) has completed a review of an establishment inspection report (EIR) covering a pre-approval inspection (PAI) and GMP inspection, conducted by (b) (4)-DO investigators (b) (4) at the (b) (4) facility. DGMPA has also reviewed the firm's written response (dated November 15 and 19, 2013) to the FDA Form-483 observations. This inspection was initiated by (b) (4)-DO to provide pre-approval coverage of NDA 22396.

(b) (4)

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immediately following this page

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JUANDRIA WILLIAMS  
12/17/2013

MAHESH R RAMANADHAM  
12/17/2013



NDA 022396

**DISCIPLINE REVIEW LETTER**

Javelin Pharmaceuticals, Inc.  
c/o Hospira, Inc.  
275 North Field Dr.  
Dept. 0392, Bldg. H2-2  
Lake Forest, IL 60045

Attention: Steven Townsend  
Associate Director, Global Regulatory Affairs

Dear Mr. Townsend:

Please refer to your December 3, 2009, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dyloject (diclofenac sodium) Injection.

We also refer to your resubmission dated June 28, 2013, which contained revised carton and container labels.

Our review of the carton and container labels is complete, and we have identified the following deficiencies:

**Carton and Container Labels**

- a. Ensure the established name is printed in letters that are at least half as large as the letters comprising the proprietary name and has commensurate prominence with the proprietary name taking into consideration all factors including typography, layout, contrast, and other printing features pursuant to 21 CFR 201.10(g)(2).
- b. Revise the proposed proprietary name "DYLOJECT" from all upper case to title case (i.e. "Dyloject") for improved readability.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at (301) 796-4085.

Sincerely,

*{See appended electronic signature page}*

Matthew Sullivan, MS  
Chief, Project Management Staff (Acting)  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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MATTHEW W SULLIVAN  
12/11/2013

**Patwardhan, Swati**

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**From:** Walker, Morgan  
**Sent:** Wednesday, December 04, 2013 11:20 AM  
**To:** Patwardhan, Swati  
**Subject:** RE: carton and container labeling comments from DMEPA- NDA 022396 Dyloject

Hi Swati,

Some of them are still relevant. Please include the following comments in your letter:

A. Comments to the Division

a. Package Insert

i. FDA launched a campaign in conjunction with ISMP to prevent the use of error-prone abbreviations. As part of this campaign, the FDA agreed not to approve error prone abbreviations in labeling because they are carried on to the prescribing practice. Therefore,

we request you revise the abbreviation 'IV' to read 'Intravenous' throughout the package insert. The abbreviation 'IV' is considered error-prone<sup>2</sup> as it can be misinterpreted for other routes of administration.

ii. In the Dosage and Administration Section (Highlights and Full Prescribing Information) include the statement, "For Intravenous Administration Only".

B Comments to the Applicant

a. Container Labels

i. Ensure the established name is printed in letters that are at least half as large as the letters comprising the proprietary name and has commensurate prominence with the proprietary name taking into consideration typography factors pursuant to 21 CFR 201.10(g)(2).

ii. Revise the proposed proprietary name "DYLOJECT" from all upper case to title case (i.e. Dyloject) for improved readability.

b. Carton Labeling

i. See Comments B(a)(i) and B(a)(ii) above and apply to carton labeling.

Sorry for the confusion and I hope this helps clarify everything. Please let me know if you have additional questions.

Thanks,

Morgan

---

**From:** Patwardhan, Swati  
**Sent:** Wednesday, December 04, 2013 10:46 AM  
**To:** Walker, Morgan  
**Cc:** Skarupa, Lisa; Kapoor, Rachna  
**Subject:** RE: carton and container labeling comments from DMEPA- NDA 022396 Dyloject

Hi Morgan,

I am in process of drafting the discipline review letter for DMEPA labeling comments for Dyloject- NDA 022396 and noticed that the container and carton labels referenced in the DMEPA review are not the same that were submitted in the resubmission dated June 28, 2013.

Therefore, the comments provided in the DMEPA review do not seem relevant to the current carton and container labels. Can you please help clarify

Please attached find DMEPA review dated 11/8 and also find below the links for carton and container labels submitted in resubmission dated 06/28/2013.

<\\cdsesub1\evsprod\nda022396\0039\m1\us\container.pdf>

<\\cdsesub1\evsprod\nda022396\0039\m1\us\carton.pdf>

I was planning to send the letter today, but I will hold off until I hear back from you.

Thank you

Swati Patwardhan  
Phone: 301-796-4085

---

**From:** Walker, Morgan  
**Sent:** Monday, December 02, 2013 6:41 PM  
**To:** Patwardhan, Swati; Kapoor, Rachna  
**Cc:** Skarupa, Lisa  
**Subject:** RE: carton and container labeling comments from DMEPA

We concur.

Thanks,

Morgan

---

**From:** Patwardhan, Swati  
**Sent:** Monday, December 02, 2013 4:11 PM  
**To:** Kapoor, Rachna; Walker, Morgan  
**Cc:** Skarupa, Lisa  
**Subject:** RE: carton and container labeling comments from DMEPA

Hi Morgan,

Can you please review the CMC's recommendation fro [vial storage](#)?  
Let me know if you concur with their recommendation.

Thank you

Swati Patwardhan  
Phone: 301-796-4085

---

**From:** Patwardhan, Swati  
**Sent:** Tuesday, November 26, 2013 5:50 PM  
**To:** Kapoor, Rachna  
**Cc:** Skarupa, Lisa; Walker, Morgan  
**Subject:** RE: carton and container labeling comments from DMEPA

Hi Rachna,  
As I see the CMC reviewer's comment is for including the following (b) (4)

(b) (4)

Are you ok with it?

Thank you

Swati Patwardhan  
Phone: 301-796-4085

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**From:** Kapoor, Rachna  
**Sent:** Tuesday, November 26, 2013 9:49 AM  
**To:** Patwardhan, Swati  
**Cc:** Skarupa, Lisa; Walker, Morgan  
**Subject:** RE: carton and container labeling comments from DMEPA

Hi Swati,

I agree that the carton should have the full info on it as stated below.

thanks

*Rachna*

**Rachna Kapoor, Pharm.D.**  
Safety Evaluator  
Division of Medication Error Prevention and Analysis  
FDA/CDER/OSE/OMEPRM/DMEPA

Phone: (240) 402-0217  
Fax: (301) 796-9865  
Rachna.Kapoor@fda.hhs.gov

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**From:** Patwardhan, Swati  
**Sent:** Monday, November 25, 2013 12:15 PM  
**To:** Kapoor, Rachna  
**Cc:** Skarupa, Lisa  
**Subject:** FW: carton and container labeling comments from DMEPA

Hi Rachna,  
Please see comments from CMC regarding storage comment.  
Let me know if you agree.  
Thank you

Swati Patwardhan  
Phone: 301-796-4085

---

**From:** Peri, Prasad  
**Sent:** Monday, November 25, 2013 12:05 PM  
**To:** Patwardhan, Swati; Pinto, Julia; Lloyd, Joshua; Emami, Armaghan; Xu, Yun (CDER); Nallani, Srikanth; Wasserman, Adam; Derr, Janice  
**Subject:** RE: carton and container labeling comments from DMEPA

Swati,  
I am OK with these comments. [REDACTED] (b) (4)  
[REDACTED] See if DMEPA thinks this is possible.

However can we compromise if possible of keeping only the following: [REDACTED] (b) (4)  
[REDACTED]

Prasad

---

**From:** Patwardhan, Swati  
**Sent:** Monday, November 25, 2013 11:40 AM  
**To:** Peri, Prasad; Pinto, Julia; Lloyd, Joshua; Emami, Armaghan; Xu, Yun (CDER); Nallani, Srikanth; Wasserman, Adam; Derr, Janice  
**Subject:** RE: carton and container labeling comments from DMEPA

This is for NDA 022396- Dyloject

Swati Patwardhan  
Phone: 301-796-4085

---

**From:** Patwardhan, Swati

**Sent:** Monday, November 25, 2013 10:51 AM

**To:** Galati, Steven; Pinto, Julia; Lloyd, Joshua; Emami, Armaghan; Xu, Yun (CDER); Nallani, Srikanth; Wasserman, Adam; Derr, Janice

**Subject:** carton and container labeling comments from DMEPA

Greetings!

DMEPA has completed their review of carton and container has following comments to be conveyed to Sponsor:

- i. Container Labels
  - a. Ensure the established name is printed in letters that are at least half as large as the letters comprising the proprietary name and has commensurate prominence with the proprietary name taking into consideration typography factors such as the font weight, pursuant to 21 CFR 201.10(g)(2)
  - b. Revise the proposed proprietary name "DYLOJECT" from all upper case to title case (i.e. Dyloject) for improved readability.
  - c. Remove the (b)(4) information, (b)(4) (b)(4) from the principal display panel, as it is not required by small label regulations and crowds the label, making it difficult to read other required product information
  - d. Revise and increase the prominence of the route of administration statement, (b)(4) to read, 'For Intravenous Use Only'.
- ii. Carton Labeling
  - a. See Comments B(a)(i) and B(a)(ii) above and apply to carton labeling
  - b. Include the statement, 'Single-Use Vials, Discard Unused Portion' on the principal display panel
  - c. Relocate the net quantity statement, '25 x 1 mL Vials', to appear below the statement, 'For Intravenous Use' to move it away from the strength statement to prevent confusion between the strength and number of vials

Let me know if you agree or have any edits. I will alsodraft DR letter for these comments.

Carton and container is in EDR: <\\cdsesub1\evsprod\nda022396\0039\m1\us\>

Thank you

Swati Patwardhan

Regulatory Health Project Manager

Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Center of New Drug Evaluation and Research

Phone: 301-796-4085

Fax: 301-796-9748

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/s/  
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SWATI A PATWARDHAN  
12/05/2013

**PeRC PREA Subcommittee Meeting Minutes  
November 6, 2013**

**PeRC Members Attending:**

Lynne Yao  
Robert Nelson  
Hari Cheryl Sachs  
Karen Davis-Bruno  
Rosemary Addy  
Patricia Dinndorf  
Julia Pinto  
William J. Rodriguez  
Peter Starke  
Wiley Chambers  
Lily Mulugeta  
Daiva Shetty  
Andrew Mosholder  
Gregory Reaman  
Barbara Buch  
Martha Nguyen  
Dianne Murphy  
Jane Inglese

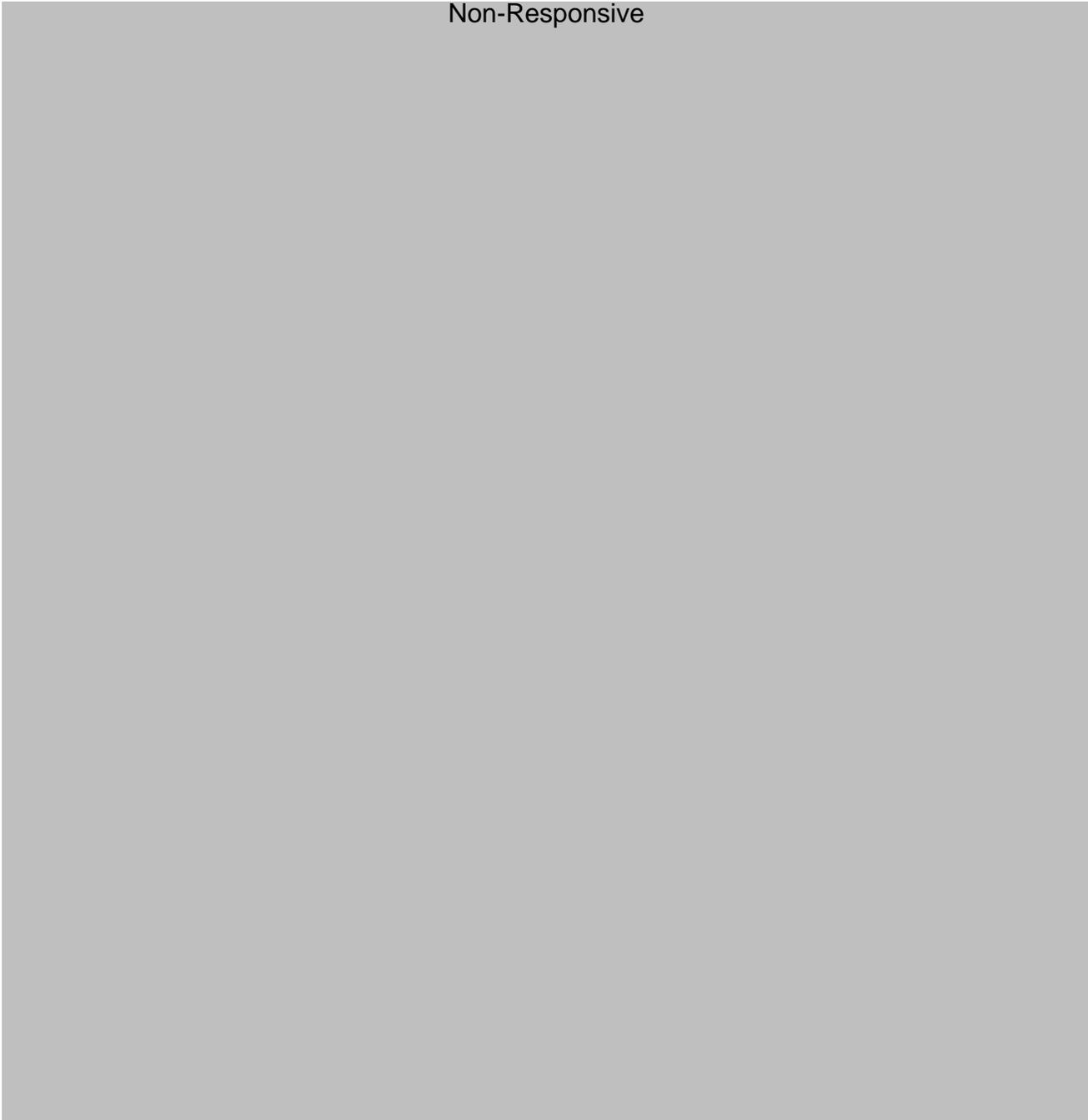
**Guests Attending:**

Nichella Simms (PMHS)  
Erica Radden (PMHS)  
Donna Snyder (PMHS)  
Kimberly Compton (DAAAP)  
Ellen Fields (DAAAP)  
Srikanth Nallani (DAAAP)  
Sofia Chaudhry (DPARP)  
Susan Limb (DRPAR)  
Satjit Brar (OCP)  
Sandy Chang (DPP)  
Glenn Mannheim (DPP)  
Jing Ahang (DPP)  
Lawren Slate (OCP)  
Carla Epps (DGIEP)  
David Joseph (DGIEP)  
Rigo Roca (DAAAP)  
William Chong (DMEP)  
Todd Bourcier (DMEP)  
Josh Lloyd (DAAAP)  
Mukesh Summan (DMEP)

Swati Patwardhan (DAAAP)  
Brittany Goldberg (DAVP)  
Katherine Schumann (DAVP)  
Yodit Belew (DAVP)  
Karen M. Mahoney (DMEP)  
Manoj Khurana (OCP)  
Lokesh Jain (OCP)

**Agenda**

11:00	NDA		Non-Responsive
11:15	NDA	22396	Dyloject (diclofenac) Partial Waiver/Deferral/Plan
11:30	NDA		Non-Responsive
11:45	NDA		
	NDA		
	NDA		



Non-Responsive

## Non-Responsive

### **Dyloject (diclofenac) Partial Waiver/Deferral/Plan**

- NDA 22396 seeks marketing approval for Dyloject (diclofenac) for management of acute mild to moderate pain, and management of acute moderate to severe pain alone or in combination with opioid analgesics.
- The application was resubmitted on June 28, 2013, and has a PDUFA goal date of December 28, 2013.
- The application triggers PREA as directed to a new dosage form.
- On September 1, 2010, the Division discussed the pediatric study plan with the PeRC, and the Division subsequently provided comments to the sponsor. The current pediatric study plan contains the revisions reflecting those comments.
- A partial waiver is being requested for pediatric patients aged birth to less than 12 months because the product would be ineffective and/or unsafe in this age group.
- *Division justification for waiver:* The published literature documents great inter-individual variability in multiple pharmacokinetic parameters for diclofenac in neonates and young children due to immaturity of metabolic pathways. Given this variability, it is highly unlikely that additional studies will result in dosage recommendations that could be safely generalized and applied across individuals in younger pediatric age groups.
- A deferral is being requested for pediatric patients aged 1 to less than 17 years because adult studies are completed and the product is ready for approval.
- The sponsor proposes to conduct the following studies:
  - Study 1: An open-label pharmacokinetic and safety study or studies of an age-appropriate formulation of Dyloject in pediatric patients 2 to <17 years of age with acute pain
  - Study 2: A pharmacokinetic, safety, and efficacy study or studies of an age-appropriate formulation of Dyloject in pediatric patients 1 to <2 years of age with acute pain
  - The sponsor will need to provide updated dates as the pediatric study plan was submitted during the first review cycle
- *PeRC Recommendations:*
  - The PeRC had a lengthy discussion regarding potential paths for pediatric development under PREA. The PeRC noted that there was no evidence of a serious safety signal in pediatric patients, however other NSAIDs more commonly use in children such as ibuprofen and metabolized in a similar manner may have a safety profile.. Additionally, the PeRC noted that variability in development of metabolic pathways for this product have not yet been clearly established and would not preclude studies in infants 0 to 1 year of age. Therefore, the PeRC and the Division concluded that partial waiver of studies in patients less than one year of age should not be granted at this time.

However, due to potential safety/efficacy/dosing concerns raised by the issues described above, PeRC recommends a stages approach to fulfillment of PREA requirements with older patients to be studied first. If studies in older patients reveal safety concerns then studies in younger patients could be waived. Additionally, if other more commonly used NSAIDS receive approval down to birth then waiver for studies in patients less than one year of age could also be considered at that time.

- The PeRC recommended that the Division ask the sponsor to amend the pediatric plan to request a deferral of studies for pediatric patients aged 0 to less than 17 years.
- The PeRC further recommended that the Division issue discrete PMRs for each pediatric age group having sequential, non-overlapping protocol submission and study completion dates starting with the oldest pediatric age groups and followed by progressively younger pediatric age groups. This will allow the Division to review data on the older pediatric patients before the initiation of studies in younger pediatric patients.

Non-Responsive

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/s/  
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JANE E INGLESE  
11/18/2013

**Patwardhan, Swati**

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**From:** Patwardhan, Swati  
**Sent:** Thursday, November 07, 2013 5:13 PM  
**To:** 'Turoff, Cecilia C'  
**Subject:** RE: NDA 022396 Dyloject -Information request -Nov-7-2013

Dear Ms. Turoff,

In the complete response dated June 28, 2013, [REDACTED] (b) (4)  
[REDACTED] Please provide the location [REDACTED] (b) (4)  
[REDACTED] within your NDA application.

Thank you

Swati Patwardhan  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)  
Center of New Drug Evaluation and Research  
Phone: 301-796-4085  
Fax: 301-796-9748

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SWATI A PATWARDHAN  
11/07/2013

**Patwardhan, Swati**

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**From:** Patwardhan, Swati  
**Sent:** Tuesday, November 05, 2013 3:03 PM  
**To:** 'Turoff, Cecilia C'  
**Subject:** RE: NDA 022396 Dyloject -Information request -Nov-5-2013

Dear Ms. Turoff,

We refer to your amendment dated October 31, 2013 containing revised pediatric study plan containing revised timelines for the pediatric studies.

Please provide the justification for needing until January 2016 for formulation development and February 2016 for Study 1 protocol submission.

We request a response preferably by end of this week. Let me know if the requested turnaround time is not feasible at your end.

Thank you

Swati Patwardhan  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)  
Center of New Drug Evaluation and Research  
Phone: 301-796-4085  
Fax: 301-796-9748

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/s/  
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SWATI A PATWARDHAN  
11/05/2013

**Patwardhan, Swati**

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**From:** Patwardhan, Swati  
**Sent:** Monday, October 28, 2013 11:13 AM  
**To:** 'Turoff, Cecilia C'  
**Subject:** RE: NDA 022396 Dyloject (Diclofenac Sodium)

Dear Ms. Turoff,

We are reviewing your resubmission for Dyloject NDA 022396 submitted June 28, 2013 and request additional information as follows:

1. Submit certification of deferral for pediatric studies for this application.
2. A revised Pediatric Study Plan was submitted on September 27, 2010 towards fulfilling PREA requirement. The dates submitted in the PSP for study Phase 3 Safety, PK (DFC-012) are not current. Please submit revised dates.

Let me know if you have any questions.

Thank you

Swati Patwardhan  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)  
Center of New Drug Evaluation and Research  
Phone: 301-796-4085  
Fax: 301-796-9748

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/s/  
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SWATI A PATWARDHAN  
10/28/2013



NDA 022396

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Hospira, Inc.  
275 North Field Drive  
Building H2-2  
Lake Forest, IL 60045

ATTENTION: Cecilia C. Turoff  
Senior Associate Global Regulatory Affairs

Dear Ms. Turoff:

Please refer to your New Drug Application (NDA) dated December 2, 2009, received December 3, 2009, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Diclofenac Sodium Injection 37.5 mg/mL.

We also refer to your correspondence, dated and received July 30, 2013, requesting review of your proposed proprietary name, Dyloject. We have completed our review of the proposed proprietary name, Dyloject and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your July 30, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Lisa Skarupa, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2219. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Swati Patwardhan, at (301) 796-4085.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
10/11/2013



NDA 022396

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

Hospira, Inc.  
275 North Field Dr.  
Dept. 0392, Bldg. H2-2  
Lake Forest, IL 60045

Attention: Cecilia C. Turoff  
Senior Associate, Global Regulatory Affairs

Dear Ms. Turoff:

We acknowledge receipt of the resubmission submitted and received June 28, 2013, of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Dyloject (diclofenac sodium) Injection.

We consider this a complete, class 2 response to our October 1, 2010, action letter. Therefore, the user fee goal date is December 28, 2013.

If you have any questions, contact Swati Patwardhan, Regulatory Project Manager, at (301) 796-4085.

Sincerely,

*{See appended electronic signature page}*

Matt Sullivan, MS  
Chief, Project Management Staff (acting)  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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MATTHEW W SULLIVAN  
07/12/2013



NDA 022396

**ACKNOWLEDGE CORPORATE  
ADDRESS CHANGE**

Hospira Inc  
275 North Field Dr.  
Dept. 0389, Bldg. H2-2  
Lake Forest, IL 60045

Attention: Laurie Wojtko  
Sr. Associate, Global Regulatory Affairs

Dear Ms Wojtko:

We acknowledge receipt on November 9, 2011, of your November 8, 2011 correspondence notifying the Food and Drug Administration (FDA) that the corporate address has been changed from

125 Cambridge Park Drive  
Cambridge, MA 02140

to

275 North Field Dr.  
Dept. 0389, Bldg. H2-2  
Lake Forest, IL 60045

for the following new drug application (NDA):

NDA 022396 for Dyloject (diclofenac sodium) Injection

We have revised our records to reflect this change.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthesia, Analgesia, and Addiction Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call me, at (301) 796-1298.

Sincerely,

*{See appended electronic signature page}*

Sara E. Stradley, MS  
Chief, Project Management Staff  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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SARA E STRADLEY  
01/08/2013

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**From:** [Davies, Kathleen](#)  
**To:** ["Tucker, Roberta":](#)  
**Subject:** Dyloject: follow up to IR on anticoagulant use  
**Date:** Wednesday, September 22, 2010 3:52:00 PM

---

Hi Robbie,

We note that in your response to our IR related to the use of anticoagulating agents from Sept 17, 2010, you indicated that in your safety database (safety population 1) a total of 483/587 subjects in study DFC-010 had total hip or knee replacement surgery and received anticoagulant therapy and Dyloject concomitantly compared with 19/55 subjects from the controlled study DFC-005. Given that the vast majority of the enrolled patients were treated with the study medication following major abdominal, spinal, and orthopedic surgeries, provide explanation of the methods utilized for prophylaxis of pulmonary embolism and deep vein thrombosis in the participants in studies DFC-005, DFC-004, and DFC-010 who were not receiving anticoagulating agents.

Additionally, provide description of the methods for DVT and PE prophylaxis that were used in the following subjects:

DFC004: 01-049

DFC-005: 08-033, 04-034, 05-108, 08-036

DFC-010: 13-072, 33-003, 47-014, 72-019, 51-002, 54-002, 51-013, 13-030, 48-018.

If you ave any questions, let me know.

Kathleen

**From:** [Davies, Kathleen](#)  
**To:** ["Tucker, Roberta":](#)  
**Subject:** RE: CV and anticoag IR response  
**Date:** Friday, September 17, 2010 3:03:00 PM

---

Hi Robbie,

Could you please clarify of the 41 patients receiving anticoagulating agents in the controlled trials, how many patients were from study DFC-004 and how many were from study DFC-005?

Thanks,  
Kathleen

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

From: Tucker, Roberta [<mailto:rtucker@javelinpharma.com>]  
Sent: Friday, September 17, 2010 10:21 AM  
To: Davies, Kathleen  
Subject: CV and anticoag IR response  
Importance: High

Dear Kathleen,

Attached please find our response to the August 31 IR requests (CV anticoagulant). I will submit these formally to the NDA next week (that is the reason for the Sept. 21,2010 date on the letter.)

regards,

Robbie

**From:** [Davies, Kathleen](#)  
**To:** ["Tucker, Roberta";](#)  
**Subject:** IBs for studies 001, 004 and 005  
**Date:** Friday, September 17, 2010 1:32:00 PM

---

Hi Robbie,

Can you please tell me the location, either in the IND or NDA, of the IBs for the 3 studies submitted to your NDA (001, 004, 005)? Alternatively, you can send me a copy of the IBs via email.

Kathleen

**From:** [Davies, Kathleen](#)  
**To:** ["Tucker, Roberta";](#)  
**Subject:** NDA 22396/Dyloject  
**Date:** Friday, September 17, 2010 1:31:00 PM

---

Hi Robbie,

Please refer to your NDA 22396 for Dyloject. We recently had your pediatric plan reviewed by the Pediatric Research Committee (PeRC) and they found your plan to waive (b) (4) and defer (b) (4) unacceptable. The recommendations of PeRC are:

1. You can waive 0 - 12 months due to safety concerns in this age group.
2. You can defer 13 months to 17 years. You should collect safety and PK from 2 to 17 since efficacy can be extrapolated for this age group. However, you must study efficacy, safety and PK in 1 - 2 years.

In addition, you must develop an age-appropriate formulation (b) (4)

Please resubmit your pediatric plan incorporating these recommendations and providing a submission date, study completion date, and final report submission date.

If you have any questions, please let me know.

Kathleen

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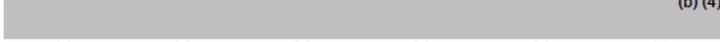
KATHLEEN M DAVIES  
09/28/2010

**From:** [Davies, Kathleen](#)  
**To:** ["Tucker, Roberta";](#)  
**Subject:** Dyloject - Stability  
**Date:** Friday, September 03, 2010 1:39:00 PM

---

Hi Robbie,

The proposed post-approval stability commitment for drug product stability states

 (b) (4)  
Please  
revise your stability commitment  (b) (4)  
and submit this to your NDA.

Kathleen

**From:** [Davies, Kathleen](#)  
**To:** ["Tucker, Roberta";](#)  
**Subject:** Dyloject IR  
**Date:** Tuesday, August 31, 2010 3:21:00 PM

---

Hi Robbie,

I have another IR for you regarding Dyloject. Please provide a response as soon as possible.

*From your Table 4-50 p 162 in the ISS report (Appendix 13.5, Table 3.12.1.2.2.) we note that in the controlled trials DFC-004 and DFC-005, 41 out of 608 patients were receiving anticoagulation therapy, whereas in the open label study DFC-010, 601 out of 969 patients were receiving anticoagulation therapy. We also note that the majority of patients participating in both controlled and uncontrolled studies were post-operative patients following major orthopedic, abdominal, and pelvic surgeries. Provide explanation for the discrepancy in use of anticoagulating agents within the clinical development program. If relevant, include explanation of study enrollment criteria, study conduct, and variability in patterns of clinical practice. Provide explanation of the timing for initiation of anticoagulation therapy in relation to the study treatment during the course of the controlled and uncontrolled studies.*

Thanks,

Kathleen

**From:** [Davies, Kathleen](#)  
**To:** ["Tucker, Roberta"](#);  
**Subject:** IR follow up on recall for Dyloject - please respond  
**Date:** Tuesday, September 07, 2010 2:18:00 PM

---

Hi Robbie,

The review team for Dyloject requests a response by tomorrow on two specific items (b) (4) We are aware there is an expected response in writing next week, but it is critical we know these two items right away and how it impacts the NDA. We request a response by tomorrow, Wed, on these items, via email.

Confirm:

1. (b) (4)  
(b) (4) and
2. (b) (4)

If you have any questions, let me know.

Kathleen

**From:** [Davies, Kathleen](#)  
**To:** ["Tucker, Roberta";](#)  
**Subject:** IR for Dyloject  
**Date:** Tuesday, August 31, 2010 11:00:00 AM

---

Hi Robbie,

I have an additional clinical request for Dyloject:

*Provide the narratives or any information (e.g., age, background risk factors, concomitant meds, final outcome) on the following 4 patients who had cardiovascular event of interest:*

*Subject 47-014: coronary atherosclerosis; Subjects 53-014 and 72-006: angina pectoris; and Subject 69-021: myocardial ischemia.*

Thanks,

Kathleen

**From:** [Davies, Kathleen](#)  
**To:** ["Tucker, Roberta";](#)  
**Subject:** NDA 22396/Dyloject - follow up on IRs  
**Date:** Monday, August 30, 2010 12:48:00 PM

---

Hi Robbie,

I wanted to follow up on the 2 IRs sent last week and when we should expect a response.

Kathleen

**From:** [Davies, Kathleen](#)  
**To:** ["Tucker, Roberta";](#)  
**Subject:** RE: IR request for Dyloject  
**Date:** Friday, September 03, 2010 11:14:00 AM

---

Hi Robbie,

Thanks for the update. We will need this information as soon as possible since the application due date is quickly approaching. I recognize that some people are unavailable to answer questions; however, please keep in mind that we need this as fast as possible.

[REDACTED] (b) (4)

Kathleen

---

**From:** Tucker, Roberta [mailto:rtucker@javelinpharma.com]  
**Sent:** Tuesday, August 31, 2010 7:08 PM  
**To:** Davies, Kathleen  
**Subject:** RE: IR request for Dyloject  
**Importance:** High

Dear Kathleen,

I promised to get back to you regarding the timing of submission of information on [REDACTED] (b) (4) our response to the Division's renal impairment request for information.

1. [REDACTED] (b) (4)

[REDACTED] (b) (4)

2. Regarding the information you requested on renal impairment:

We are presently working on the response. The medical person responsible is out of the country and will be returning next Monday. We hope to be able to send you a response by Sept. 10 (the end of next week) but the latest we will provide you the information requested is the week of September 13.

We are aware of the time until the action date and are working to complete responses to all your recent requests as soon as possible. We hope to be able to provide responses to all outstanding requests no later than the week of Sept 13. We will make every effort to complete the responses sooner if possible. If you have any questions, please don't hesitate to contact me by email or phone at 508 688-2026..

Regards,

Robbie Tucker

---

**From:** Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]  
**Sent:** Wed 8/25/2010 11:16 AM  
**To:** Tucker, Roberta  
**Subject:** IR request for Dyloject

Hi Robbie,

Please refer to your NDA 22396 for Dyloject. We have two requests for information regarding this NDA:

1. We had requested (when I was on leave so bear with me on the summary), information [REDACTED] (b) (4)

[REDACTED] My chemistry reviewer notes that this information has not yet been submitted to the NDA. Please provide an update on this information.

2. We note that in your clinical development program at least 11 cases of acute renal failure were observed with exposure to DIC075V in patients with and without previous history of renal impairment. This number of acute renal failures occurring within the size of your clinical development program is concerning. We also note that the UK (Therabel Pharma UK) label for Dyloject TM contraindicates use of IV Dyloject in patients with moderate and severe renal impairment or in patients with

hypovolemia and dehydration from any cause. Provide the data supporting the contraindication for Dyloject TM in patients with renal impairment listed in the UK label. Also, provide your rationale for why you did not plan to contraindicate DIC075V for patients with moderate or severe renal impairment in your proposed US label.

If you have any questions, please let me know.

Kathleen

**From:** [Davies, Kathleen](#)  
**To:** ["Tucker, Roberta";](#)  
**Subject:** revised IR  
**Date:** Wednesday, August 25, 2010 1:05:00 PM

---

Hi Robbie,

There is a slight revision to the IR I sent earlier today. Please see below:

*We note that in your clinical development program at least 11 cases of acute renal failure were observed with exposure to DIC075V in patients with and without previous history of renal impairment. This number of acute renal failures occurring within the size of your clinical development program is concerning. We also note that the UK (Therabel Pharma UK) label for Dyloject TM contraindicates use of IV Dyloject in patients with moderate and severe renal impairment or in patients with hypovolemia and dehydration from any cause. Provide the data supporting the contraindication for Dyloject TM in patients with renal impairment listed in the UK label. Also, provide your rationale for why you did not plan to contraindicate DIC075V for patients with any degree of renal impairment (mild, moderate and severe) in your proposed US label.*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22396	ORIG-1	HOSPIRA INC	diclofenac sodium injection

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/s/

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KATHLEEN M DAVIES  
09/15/2010

**From:** [Davies, Kathleen](#)  
**To:** ["Tucker, Roberta";](#)  
**Subject:** IR request for Dyloject  
**Date:** Wednesday, August 25, 2010 11:16:00 AM

---

Hi Robbie,

Please refer to your NDA 22396 for Dyloject. We have two requests for information regarding this NDA:

1. We had requested (when I was on leave so bear with me on the summary), information (b) (4)

[REDACTED] My chemistry reviewer notes that this information has not yet been submitted to the NDA. Please provide an update on this information.

2. We note that in your clinical development program at least 11 cases of acute renal failure were observed with exposure to DIC075V in patients with and without previous history of renal impairment. This number of acute renal failures occurring within the size of your clinical development program is concerning. We also note that the UK (Therabel Pharma UK) label for Dyloject TM contraindicates use of IV Dyloject in patients with moderate and severe renal impairment or in patients with hypovolemia and dehydration from any cause. Provide the data supporting the contraindication for Dyloject TM in patients with renal impairment listed in the UK label. Also, provide your rationale for why you did not plan to contraindicate DIC075V for patients with moderate or severe renal impairment in your proposed US label.

If you have any questions, please let me know.

Kathleen

**From:** [Davies, Kathleen](#)  
**To:** ["Tucker, Roberta";](#)  
**Subject:** revised IR  
**Date:** Wednesday, August 25, 2010 1:05:00 PM

---

Hi Robbie,

There is a slight revision to the IR I sent earlier today. Please see below:

*We note that in your clinical development program at least 11 cases of acute renal failure were observed with exposure to DIC075V in patients with and without previous history of renal impairment. This number of acute renal failures occurring within the size of your clinical development program is concerning. We also note that the UK (Therabel Pharma UK) label for Dyloject TM contraindicates use of IV Dyloject in patients with moderate and severe renal impairment or in patients with hypovolemia and dehydration from any cause. Provide the data supporting the contraindication for Dyloject TM in patients with renal impairment listed in the UK label. Also, provide your rationale for why you did not plan to contraindicate DIC075V for patients with any degree of renal impairment (mild, moderate and severe) in your proposed US label.*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22396	ORIG-1	HOSPIRA INC	diclofenac sodium injection

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/s/

KATHLEEN M DAVIES  
08/26/2010

# MEMORANDUM OF INTERNAL MEETING

DATE: July 8, 2010

APPLICATION NUMBER: NDA 22-396, Diclofenac Sodium

SUBJECT: Environmental exclusion for NDA 22-396

Internal meeting requested by Prasad Peri with Environmental Assessment Group and ONDQA.

Attendees: ONDQA:

- Eric Duffy Division Director, DNDQA III
- Prasad Peri, Acting Branch Chief, Br. VIII, DNDQAIII
- Danae Christodoulou, CMC Lead, Br. VIII, DNDQAIII
- Haber Martin, CMC reviewer, Br. VIII, DNDQAIII
- Swati Patwardhan, Reg. Project Manager, DNDQAIII

OPS/EA

- Ranaan Bloom, Toxicologist
- Emily McVey, Toxicologist

Background:

NDA 22-396, diclofenac sodium was submitted on December 3, 2009. The applicant has requested categorical exclusion from environmental assessment based on limited amount of drug produced but did not state absence of any significant environmental issues. They claim that the expected introduction concentration is less than the 1 ppb. Dr. Martin pointed to the recent published literature (Nature **2004**, 427, 630-633 and Environ. Sci. Technol. **2010**, 44, 2176-2182) which indicated that diclofenac has a potential for serious harm to the environment due to toxicity to birds and fish.

Meeting Summary:

ONDQA and Environmental Assessment group (EA) agreed that an environmental exclusion could not be granted based on the published literature and supporting data will be required from the applicant to waive the assessment. If necessary, an interim waiver can be granted during NDA approval, coupled with a post-marketing requirement to complete environmental assessment studies. It was agreed that the applicant should be requested to provide additional consideration to support the request for categorical exclusion, in terms of literature assessment of impact to the environment and comparison of impact from exposure of their product.

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Swati Patwardhan  
Regulatory Health Project Manager  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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Concurrence  
Danae Christodoulou  
CMC Lead, Br. VIII,  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22396	ORIG-1	HOSPIRA INC	diclofenac sodium injection

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/s/

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SWATI A PATWARDHAN  
08/19/2010

DANAE D CHRISTODOULOU  
08/19/2010  
For Prasad Peri

**Stradley, Sara**

---

**From:** Stradley, Sara  
**Sent:** Friday, August 06, 2010 1:20 PM  
**To:** 'Tucker, Roberta'  
**Cc:** Stradley, Sara  
**Subject:** NDA 22396 IR Aug 6

Hi Robbie

We have the following IR request:

1. Please submit the screening, baseline, and all follow-up ECGs for the following 3 subjects: Subject 61-001, Subject 74-002 and Subject 24-021.

2. For consistency, please complete the following summary table for adverse events for the pooled controlled trials DFC-004 and 005 and the open label study DFC-010 as well as list the reference source tables for these data.

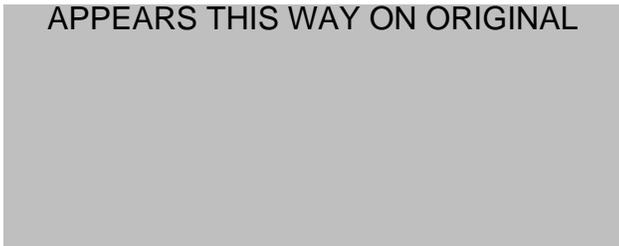
	Placebo (N=126) n (%)	DIC075V		
		DFC-004 and DFC-005 (N=187) n(%)	DFC-010 (N=969) n (%)	Total (N=1156) n (%)
Number of Subjects with Any AE:				
Number of Subjects with Any Treatment-Emergent AE:				
Number of Subjects with Any SAE:				
Number of Subjects with any Treatment - Emergent SAE:				
Number of Subjects with Any Severe AEs:				
Number of Subjects with any Treatment-Emergent Severe AEs:				
Deaths:				
Number of Subjects with AEs Leading to Withdrawal:				
Number of Subjects with Treatment - Emergent AEs Leading to Withdrawal				

If possible, please send the information by email by August 11 with a follow-up formal submission to the NDA.

*Sara E. Stradley, MS*  
Chief, Project Management Staff  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Office of New Drugs  
Center for Drug Evaluation and Research  
**phone # 301-796-1298**  
**fax # 301-796-9713**

email: [sara.stradley@fda.hhs.gov](mailto:sara.stradley@fda.hhs.gov)

APPEARS THIS WAY ON ORIGINAL



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22396	ORIG-1	HOSPIRA INC	diclofenac sodium injection

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/s/

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SARA E STRADLEY  
08/06/2010

This is a memo to note that the Transfer of Ownership Letter dated July 23, 2010 contained a mistake.

Name of Drug Product: Dyloject™ (diclofenac sodium) Injection  
NDA Number: 022396  
Name of New Applicant: Hospira, Inc.  
Name of Previous Applicant: Javelin Pharmaceuticals, Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate (b) (4) as the applicant of record for this application.

It should read:

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate **Hospira, Inc.** as the applicant of record for this application.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22396	GI-1	HOSPIRA INC	diclofenac sodium injection

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/s/

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SARA E STRADLEY  
08/05/2010



NDA 022396

**ACKNOWLEDGE TRANSFER NDA OWNERSHIP**

Hospira, Inc.  
125 Cambridge Park Drive  
Cambridge, MA 02140

Attention: Roberta Tucker, R.Ph.  
Regulatory Affairs

Dear Ms. Tucker:

We acknowledge receipt on July 9, 2010, of your July 8, 2010, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug Product: Dyloject™ (diclofenac sodium) Injection

NDA Number: 022396

Name of New Applicant: Hospira, Inc.

Name of Previous Applicant: Javelin Pharmaceuticals, Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate [REDACTED] <sup>(b) (4)</sup> as the applicant of record for this application.

We request that you notify your suppliers and contractors who have DMFs referenced by your application of the change in ownership so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthesia and Analgesia Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-1298.

Sincerely,

*{See appended electronic signature page}*

Sara Stradley  
Chief, Project Management Staff  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

cc: Javelin Pharmaceuticals, Inc.  
125 Cambridge Park Drive  
Cambridge, MA 02140

Application  
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JAVELIN  
PHARMACEUTICA  
LS INC

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diclofenac sodium injection

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/s/  
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SARA E STRADLEY  
07/23/2010

## Stradley, Sara

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**From:** Stradley, Sara  
**Sent:** Wednesday, July 21, 2010 9:33 AM  
**To:** 'Tucker, Roberta'  
**Subject:** July 21 IR/Dyloject

Hi Robbie

We have the following Information Request:

In order for the Agency to approve the use of drug substance from both proposed manufacturing sites, (b)(4) in the drug product, you must submit comparative analytical data listed in tabular form demonstrating that drug substance manufactured at both sites are comparable in quality/purity and that they meet the exact same newly revised specifications for parenteral grade drug substance as listed in the NDA. In addition, both manufacturing sites should use the same manufacturing process which may require amendments of the respective DMFs. If possible, submit an amendment to revise your current NDA as described above. Alternatively, you may submit this change as a post approval supplement with the supportive data and amended DMFs.

*Sara E. Stradley, MS*  
Chief, Project Management Staff  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Office of New Drugs  
Center for Drug Evaluation and Research  
phone # 301-796-1298  
fax # 301-796-9713  
email: [sara.stradley@fda.hhs.gov](mailto:sara.stradley@fda.hhs.gov)

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/s/  
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SARA E STRADLEY  
07/22/2010

## Stradley, Sara

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**From:** Stradley, Sara  
**Sent:** Friday, July 09, 2010 10:44 AM  
**To:** 'Tucker, Roberta'  
**Cc:** Stradley, Sara  
**Subject:** NDA 22396/Dyloject/IR for July 9

Hi Robbie

The Agency cannot grant a categorical exclusion for this application and we require you to submit an Environmental Assessment (EA) to address potential environmental impacts from the use of diclofenac. The exclusion cannot be granted because of information available to the Agency that warrants the preparation of an EA under FDA's "extraordinary circumstances " provision (21 CFR 25.21).

Specifically, a recent publication indicates that diclofenac has a potential for harm to the environment at environmentally-relevant concentrations (Environ. Sci. Technol. 2010, 44, 2176-2182). Other publications show hypertoxic break-down products of diclofenac and vitallogenin induction (Environmental Pollution 158 (2010) 1461–1466, Chemosphere 67 (2007) 2115–212). In addition, diclofenac has been demonstrated to be highly toxic to certain bird species (e.g., Nature 2004, 427, 630-633).

An EA typically addresses the potential for effects to sensitive species at environmentally relevant concentrations by comparing dose-response information to predicted environmental concentrations due to patient use of the applicant's drug applications. The EA for this NDA will be expected to evaluate the contribution of diclofenac from your product to the overall environmental burden of diclofenac. When preparing the EA for this application consider the potential impact of the disposal of the product remaining in the vial after its use. Information from the open literature and, if available, ecotoxicity study results may be utilized. **The Agency will review your information and determine if a Finding of No Significant Impact can be issued for your NDA application.**

We recognize that the application is already at month 7 of the review clock. Please respond as soon as possible to allow for a complete review of the EA. The Agency's EA and CMC staff are available for a meeting or Tcon to discuss this issue with you.

*Sara E. Stradley, MS*  
Chief, Project Management Staff  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Office of New Drugs  
Center for Drug Evaluation and Research  
phone # 301-796-1298  
fax # 301-796-9713  
email: sara.stradley@fda.hhs.gov

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/s/  
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SARA E STRADLEY  
07/09/2010

**Jani, Parinda**

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**From:** Jani, Parinda  
**Sent:** Thursday, July 01, 2010 1:07 PM  
**To:** 'rtucker@javelinpharma.com'  
**Subject:** FW: Dyloject impurity

Dear Robbie:

I am covering for Kathleen and Sara and I have the following "information Request" from the Pharm/tox reviewer. Please respond ASAP.

The proposed specification for the drug product impurity, (b) (4) is set at not more than (b) (4) % w/w. The maximum amount observed in the stability program to date is (b) (4) % w/w. This exceeds ICH Q3B threshold level for qualification (for (b) (4) maximum daily dose, the qualification threshold would be (b) (4) % or (b) (4) TDI which ever is lower). While you have conducted genotoxic qualification for the impurity you have not provided general toxicity qualification (in one species) to support the safety of the (b) (4) impurity. This may be addressed by the following:

1. Reduce specification of this impurity to comply with ICHQ3B limits. Note that this may impact your proposed expiry date; or,
2. Provide toxicologic support for the proposed impurity specification through conduct of a repeat-dose toxicology study of 14 days or greater in a single species using the isolated impurity or, if necessary, a nonclinical batch with significant levels of the impurity; or,
3. Provide supporting information on the presence of this impurity (b) (4) in non-clinical batches (DIC075U, Lot # R&D227) which support the safety of maximal human intake of the impurity using the proposed specification

Thanks

Parinda Jani  
Chief, Project Management Staff  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Tel # (301) 796-1232 or 2280  
Fax # (301) 796-9713

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/s/  
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PARINDA JANI  
07/01/2010

**Stradley, Sara**

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**From:** Stradley, Sara  
**Sent:** Tuesday, June 22, 2010 3:16 PM  
**To:** 'Tucker, Roberta'  
**Cc:** Stradley, Sara  
**Subject:** NDA 22396-June 22, 2009

Hi Robbie

We have reviewed the information you provided in your June 10, 2010 submission.

We can not approve

(b) (4)

Sara E. Stradley, MS  
Chief, Project Management Staff  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Office of New Drugs  
Center for Drug Evaluation and Research  
phone # 301-796-1298  
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email: sara.stradley@fda.hhs.gov

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/s/  
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SARA E STRADLEY

06/23/2010

**Stradley, Sara**

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**From:** Stradley, Sara  
**Sent:** Wednesday, June 09, 2010 3:46 PM  
**To:** 'Tucker, Roberta'  
**Cc:** Stradley, Sara  
**Subject:** NDA 22396 IR-June 9

Hi Robbie

We have the following CMC information requests/comments. Please respond as soon as possible.

1. DMF (b)(4) for diclofenac sodium injectable (b)(4) as manufactured (b)(4) is inadequate.
2. Tighten the drug substance specification limits for any individual unknown related substance to NMT (b)(4)% as per ICH Q3A guidance.
3. Please confirm that (b)(4) will be used for drug product manufacturing. (b)(4)
4. The leachables study report provided in CTD 3.2.P.2.4, Appendix 4, is very unclear. Submit a revised report that includes a complete detailed scientific description of the studies done and the results obtained. If the revised report is still inadequate, additional studies on (b)(4) leachables may be required.
5. Provide typical certificates of analysis for the compendial excipients. For hydroxypropyl betadex, add microbial and endotoxin testing and limits to the compendial specification.
6. Regarding the HPLC methods (D136, D137 and D138), provide the elution times for all three components of the formulation (diclofenac, HPβCD and monothioglycerol) for all three HPLC methods. Provide evidence that the other components do not interfere with the measurements, especially with the accuracy of the impurity determination.
7. Tighten the specification limits for osmolality further in accordance with batch data from the current limits (b)(4) since this may affect the safety of the product.
8. Tighten the specification limit for the (b)(4) impurity in accordance with batch data. Also, tighten the specification limits for hydroxypropyl betadex and monothioglycerol in accordance with batch data.
9. Tighten the pH limits (b)(4)  
Provide additional explanation (b)(4)
10. Provide a statistical analysis (e.g., mean, std. dev., graphical representation of the trend etc.) (b)(4)  
(b)(4)  
Tighten specification limits in accordance with batch data.

Sara E. Stradley, MS  
Chief, Project Management Staff

Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Office of New Drugs  
Center for Drug Evaluation and Research  
**phone # 301-796-1298**  
**fax # 301-796-9713**  
**email: [sara.stradley@fda.hhs.gov](mailto:sara.stradley@fda.hhs.gov)**

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/s/  
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SARA E STRADLEY

06/09/2010

## Stradley, Sara

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**From:** Stradley, Sara  
**Sent:** Tuesday, June 08, 2010 11:49 AM  
**To:** 'Tucker, Roberta'  
**Cc:** Stradley, Sara  
**Subject:** information request-June 8, 2010

Hi Robbie

The QT-IRT is reviewing QT Study Report DFC-011. Please submit the following:

- The raw dataset (eg.xpt) had 54 subjects while analysis dataset (adecg.xpt) had 70. Please submit the additional raw dataset for the missing 16 subjects.

Thanks

*Sara E. Stradley, MS*  
Chief, Project Management Staff  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Office of New Drugs  
Center for Drug Evaluation and Research  
**phone # 301-796-1298**  
**fax # 301-796-9713**  
**email: [sara.stradley@fda.hhs.gov](mailto:sara.stradley@fda.hhs.gov)**

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/s/  
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SARA E STRADLEY

06/08/2010

## Stradley, Sara

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**From:** Stradley, Sara  
**Sent:** Thursday, June 03, 2010 8:49 AM  
**To:** 'Tucker, Roberta'  
**Cc:** Stradley, Sara  
**Subject:** NDA 22396/Information request--June 3

Hi Robbie

We have another information request-

- In Table 14.2.9, subjects who do not use any rescue medication are excluded from the calculations. Redo this table to include the entire ITT population, using a value of zero for any subject who declines rescue medication. Also, perform the same analyses for the “long stay” subgroup. Submit the code and results.
- Rerun the analyses shown in Table 11-5 using the “long stay” subgroup. Submit the code and results.

Thanks

*Sara E. Stradley, MS*  
Chief, Project Management Staff  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Office of New Drugs  
Center for Drug Evaluation and Research  
**phone # 301-796-1298**  
**fax # 301-796-9713**  
**email: [sara.stradley@fda.hhs.gov](mailto:sara.stradley@fda.hhs.gov)**

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/s/  
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SARA E STRADLEY

06/03/2010

**Stradley, Sara**

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**From:** Stradley, Sara  
**Sent:** Wednesday, May 26, 2010 2:18 PM  
**To:** 'Tucker, Roberta'  
**Cc:** Stradley, Sara; Davies, Kathleen  
**Subject:** IR request for NDA 22396/Dyloject

Hi Robbie

Please submit the following information as soon as possible. Thanks

**[Study DFC-004]**

**Submit L\_16.2.2.1.DEVIATE.SAS, L\_16.2.3.1.EXCLUDE.SAS and all data files used in these programs.**

**[Study DFC-005]**

**Submit L\_PROTDEV.SAS, L\_ISEPP.SAS, and all data files used in these programs.**

*Sara E. Stradley, MS*  
Chief, Project Management Staff  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Office of New Drugs  
Center for Drug Evaluation and Research  
**phone # 301-796-1298**  
**fax # 301-796-9713**  
**email: sara.stradley@fda.hhs.gov**

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/s/  
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SARA E STRADLEY

06/03/2010



NDA 022396

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Javelin Pharmaceuticals Inc  
125 Cambridge Park Drive  
Cambridge, Massachusetts 02140

ATTENTION: Roberta Tucker, RPh  
Vice President, Regulatory Affairs

Dear Ms. Tucker:

Please refer to your New Drug Application (NDA) dated December 2, 2009, received December 3, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diclofenac Sodium Injection, 37.5 mg/mL.

We also refer to your December 22, 2009, correspondence, received December 23, 2009, requesting review of your proposed proprietary name, Dyloject. We have completed our review of the proposed proprietary name, Dyloject and have concluded that it is acceptable.

The proposed proprietary name, Dyloject, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your December 22, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Bola Adeolu, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4264. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Jessica Benjamin at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
03/22/2010



NDA 022396

**FILING COMMUNICATION**

Javelin Pharmaceuticals, Inc.  
125 Cambridge Park Drive  
Cambridge, MA 02140

Attention: Roberta Tucker, R.Ph.  
Vice President, Regulatory Affairs

Dear Ms. Tucker:

Please refer to your new drug application (NDA) dated December 2, 2009, received December 3, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for diclofenac sodium injection for the short term management of acute moderate to severe pain.

We also refer to your submission dated December 22, 2009 and January 14, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **October 3, 2010**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 10, 2010.

During our filing review of your application, we identified the following potential review issues:

1.

[REDACTED] (b) (4)

(b) (4)



2. We note the proposed label lacks nonclinical study data, which may be due to an omission in the RLD product's label secondary to NSAID class labeling revisions; earlier labels may contain this information. You will need to submit a revised label in which you add nonclinical data to Section 8.1 and the entire Section 13. Also, provide a scientifically justified explanation for the proposed exposure margin adjustments. Exposure margin adjustment based on mg/day dosing does not appear supported by the comparative BA studies provided.

3. (b) (4)
- 

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver and deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver and/or deferral request is denied.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Bob A. Rappaport, M.D.  
Director  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22396	ORIG-1	JAVELIN PHARMACEUTICA LS INC	diclofenac sodium injection

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/s/

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RIGOBERTO A ROCA on behalf of BOB A RAPPAPORT  
02/12/2010



NDA 022396

**NDA ACKNOWLEDGMENT**

Javelin Pharmaceuticals, Inc.  
125 Cambridge Park Drive  
Cambridge, MA 02140

Attention: Roberta Tucker, R.Ph.  
Vice President, Regulatory Affairs

Dear Ms. Tucker:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: diclofenac sodium injection

Date of Application: December 2, 2009

Date of Receipt: December 3, 2009

Our Reference Number: NDA 022396

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 February 1, 2010 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthesia, Analgesia and Rheumatology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, call me at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Jessica Benjamin  
Regulatory Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
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NDA-22396

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diclofenac sodium injection

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/s/  
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JESSICA M BENJAMIN

12/16/2009



IND 65,048

Javelin Pharmaceuticals, Inc.  
125 Cambridge Park Drive  
Cambridge, MA 02140

Attention: Amy Cohen  
Director, Clinical Operations

Dear Ms. Cohen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DIC075V, diclofenac sodium IV, (b) (4)

We also refer to the teleconference between representatives of your firm and the FDA on March 10, 2008. The purpose of the meeting was to discuss the development plan and New Drug Application (NDA) submission for DIC075V.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2246.

Sincerely,

*{See appended electronic signature page}*

Lauren Tornetta, M.S., M.B.A.  
Regulatory Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE & TIME:** March 10, 2008, 3:00 p.m. – 4:00 p.m. (EST)

**CALL-IN NUMBER:** 1-866-206-0240/Passcode: 909006#

**APPLICATION:** **IND 65,048**

**PRODUCT:** DIC075V, diclofenac sodium IV (b) (4)

**INDICATION:** **Short-term management of acute pain in adults**

**SPONSOR:** **Javelin Pharmaceuticals, Inc.**

**TYPE OF MEETING:** B/Pre-NDA

**MEETING CHAIR:** Dr. Sharon, Hertz, Deputy Director, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

**MEETING RECORDER:** Lauren Tornetta, Regulatory Project Manager

<b>FDA Attendees</b>	<b>Title</b>
Sharon Hertz, M.D.	Deputy Division Director
Danae Christodoulou, Ph.D.	Pharmaceutical Assessment Lead, Chemistry
Adam Wasserman, Ph.D.	Pharmacology/Toxicology Supervisor
Asoke Mukherjee, Ph.D.	Pharmacology/Toxicology Reviewer
Lei Zhang, Ph.D.	Clinical Pharmacology Reviewer
Mary Purucker, M.D., Ph.D.	Medical Team Leader
Jin Chen, M.D., Ph.D.	Medical Reviewer
Dionne Price, Ph.D.	Statistical Team Leader
Yongman Kim, Ph.D.	Statistical Reviewer
Lauren Tornetta, M.S., M.B.A.	Regulatory Project Manager
<b>Javelin Attendees</b>	<b>Title</b>
Daniel B. Carr, MD	Chief Executive Officer / Chief Medical Officer
Fred Mermelstein, PhD	President
Curtis Wright IV, MD, MPH	Executive Vice President, Risk Management and Regulatory Affairs
Anne Kuan	Senior Director, Regulatory Affairs
Donna Madden	Manager, Nonclinical Affairs
(b) (4)	(b) (4)

**BACKGROUND:**

The investigational product, DIC075V, is an aqueous-based solution of diclofenac sodium, (b) (4) for intravenous (IV) administration for the short-term management of acute pain in adults. The IND number of DIC075V is 65,048.

**MEETING OBJECTIVES:**

The Sponsor's specific objectives for this meeting are as follows:

- To inform the Division of a forthcoming NDA submission and to gain concurrence from the Division on the format, structure, and content of the NDA submission.
- To present to the Division the summaries of the completed clinical studies and information from ongoing clinical studies that will be used to support the NDA submission.
- To present to the Division the nonclinical plan to support the NDA submission.
- To update the Division on the chemistry, manufacturing, and control plans and determine if there are any additional requirements.
- To present the proposed package insert to the Division and determine if the proposed package insert is satisfactory to the Division.
- To inform the Division that a request for a pediatric deferment will be filed in the pre-NDA information package that will include justification for this request.

**ACTION ITEMS:**

The Division to provide additional comments on whether the Sponsor should include patients with moderate renal failure in their studies.

**DISCUSSION POINTS:**

As specified by the Sponsor, discussion was focused on Questions 1, 4, 8, 11, 14, 15 and 19.

**General/Administrative:**

*Question 1.*

*In accordance with the Division's Electronic Orange Book, the appropriate referenced product for DIC075V 505(b)(2) NDA filing is the currently marketed Cataflam<sup>®</sup> (oral diclofenac potassium 50 mg immediate release tablets). Does the Division agree with Cataflam<sup>®</sup> being the reference product? (See Appendix 1, Appendix 2, and Appendix 4)*

**FDA Response:**

**Cataflam<sup>®</sup> may be used as a reference product for DIC075V. You will need to consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>).**

**If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature (including journal articles and textbooks) describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. For example, certain published literature referenced in your background package related to HPβCD formulated in Sporanox<sup>®</sup>. If you intend to rely upon this literature to support approval of your proposed 505(b)(2) application, you should identify these products as listed drugs relied upon. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.**

**In addition, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.**

Discussion:

The Sponsor clarified their reason to cite certain published literature related to HP $\beta$ CD formulated in Sporanox<sup>®</sup>, that is, to support the Renal WARNINGS section of their proposed label. The Sponsor requested clarification that, if they provide animal PK data showing HP $\beta$ CD clearance via glomerular filtration and provide human pharmacokinetic data including those in patients with mild renal impairment, that these data would be adequate support without referencing the Sporanox<sup>®</sup> label.

Dr. Hertz responded that providing such nonclinical and clinical data may be adequate support and requested that the Sponsor submit a justification for this rationale. The Sponsor acknowledged this response.

Dr. Hertz asked the Sponsor if they plan to contraindicate their product for patients with moderate renal insufficiency. The Sponsor responded that they do.

*Question 2.*

*Does the Division have any comments on the proposed outline of the NDA submission? (See Section 12)*

**FDA Response:**

**The outline of the NDA submission appears acceptable. Post-marketing safety experience with diclofenac injection marketed outside the United States should be included in the Module 2.7**

Discussion: No further discussion required.

*Question 3.*

*Does the Division agree with the breadth, depth, and strategy of the proposed literature search for identifying relevant references for this NDA submission? (See Section 12)*

**FDA Response:**

**The Safety data from literature reports related to parenteral administration of diclofenac, particularly by IV, should be included and analyzed separately from other routes of administration.**

Discussion: No further discussion required.

*Question 4.*

*Has the Division identified any missing or deficient elements in the draft package insert? (See Appendix 4)*

**FDA Response:**

**Your annotated label suggests that you are proposing to reference information from the Summary Basis of Approval (SBA) for Voltaren for support of safety and/or efficacy. We note that a 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug, may rely only on that finding as is reflected in the approved labeling for the listed drug.**

**Your annotated label also references information from the U.S. Voltaren XR package insert and the Sporanox Injection Package insert. If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.**

**Your annotated label also suggests that you are proposing to reference, [REDACTED] (b) (4) [REDACTED] These products are not listed in the Orange Book and are not approved in the United States. As such, we have no prior findings of efficacy or safety for these products and the package inserts for these products would not be suitable to support this application.**

**Discussion:**

The Sponsor acknowledged the Division's response and stated that they could limit the label to U.S. references only.

Dr. Hertz noted substantial PK differences between the reference drug, Cataflam, and the proposed IV product due to different routes of administration, which was affirmed by the Sponsor. Dr. Hertz stated that the different dosing regimen and route of administration result in differences in systemic exposure of diclofenac (particularly C<sub>max</sub>), which could significantly impact the safety profile.

The proposed IV product shows a significantly higher C<sub>max</sub> than the referenced drug; the Sponsor must adequately assess the safety. Simply referencing another label does not determine the relevance of the safety findings to the Sponsor's product in its proposed use. The Sponsor needs to focus on the relevant safety findings for this particular product.

*Question 5.*

*This parenteral product will be administered to patients by health care professionals and will not be dispensed directly to patients. Therefore, Javelin feels that child resistant packaging is not required. Does the Division agree? (See Appendix 4)*

**FDA Response:**

**Yes, we agree that child-resistant packaging may not be necessary.**

Discussion: No further discussion required.

*Question 6.*

*Because this parenteral product will be administered to patients by health care professionals and will not be dispensed directly to patients, Javelin proposes [REDACTED] <sup>(b) (4)</sup> Does the Division agree with this plan? (See Appendix 4)*

**FDA Response:**

**No.** [REDACTED] <sup>(b) (4)</sup>

Discussion: No further discussion required.

*Question 7.*

*A pediatric deferral will be requested for this NDA submission. Will the Division grant a pediatric deferral? (See Appendix 3)*

**FDA Response:**

**A pediatric deferral may be acceptable. However, a pediatric drug development plan must be proposed and submitted with the NDA to meet the requirements under PREA. Include in your request a timeline for submission of the deferred studies, including date of first enrollment, date study will be completed, and the date the completed study report will be submitted to the agency. Also, include the age range the deferral will cover.**

Discussion: No further discussion required.

*Question 8.*

*Javelin is planning to provide CDISC compliant Study Data Tabulation Module (STDM) datasets in SAS transport format for each study in this submission. Javelin is also planning to provide CDISC compliant integrated STDM datasets in SAS transport format for the Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS). The ISE and ISS databases will also be supported by providing a table of contents, data definition table, dataset descriptions, and dataset programming specifications. Is this approach sufficient for the Division?*

**FDA Response:**

**Yes, the approach appears sufficient. General comments regarding CDISC submissions are also provided at the end of the document (CDISC Data Requests to Sponsors).**

Discussion:

The Sponsor referenced the Division's general comments for "CDISC Data Requests to Sponsors / Quantitative Safety and Pharmacoepidemiology Group," and requested further clarification of the Agency's expectations, specifically regarding a DSMB. Dr. Hertz stated that the Sponsor should address each point; however, for those points which may not be applicable to this product, the Sponsor should provide an appropriate justification to explain why the point does not apply to their application.

*Question 9.*

*Javelin is planning to provide the full case report forms (CRFs) from subjects who experienced serious adverse events, deaths, or withdrawals due to adverse events. Is this approach acceptable to the Division?*

**FDA Response:**

**In addition, submit the CRFs from dropouts due to non-specific reasons such as consent withdrawn and “other.”**

Discussion: No further discussion required.

*Question 10.*

*For studies which utilized electronic case report forms (eCRFs), screen shots of the eCRFs will be provided if CRFs are to be included in this submission. Is this approach acceptable to the Division?*

**FDA Response:**

**Please clarify the question. We assume the entire CRF will be submitted as an eCRF, if this is the case, paper copies are not required. Please also confirm the eCRF software has been appropriately validated and follows the draft guidance for industry “Computerized Systems used in Clinical Investigations” (<http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0440-gdl0002.pdf>)**

Discussion: No further discussion required.

*Question 11.*

*Has the Division identified any missing or deficient elements which may lead to a refusal to accept our filing and/or prevent approval of the NDA?*

**FDA Response:**

**The safety database for DIC075V is insufficient to support filing of this NDA. Your DFC-PK-006 study clearly shows that DIC075V at the proposed dose of 37.5 mg has a substantially higher C<sub>max</sub> and a higher AUC than Cataflam 50 mg in both single-dose and multiple-dose assessments. As discussed during the EOP2 meeting, the safety database for DIC075V should consist of at least 1000 patients with multiple-dose and multiple-day exposure if the bioavailability of DIC075V exceeds that of Cataflam. You propose to include a total of only 360 patients who have been exposed to multiple doses of DIC075V. We will not be able to adequately assess the safety of this formulation of diclofenac with the limited exposure you propose.**

Discussion:

Dr. Hertz cited the EOP2 meeting minutes noting the safety database requirements for DIC075V. Dr. Hertz noted, as stated in the EOP2 minutes, that the Cmax and AUC for DIC075V are notably higher than other diclofenac products, which presents a safety concern.

The Sponsor stated that they have data from subjects in multi-dose PK studies and asked if these subjects could count toward the safety database requirement of 1000 patients, as defined by the Division. Dr. Hertz asked how many of these subjects there were and whether these patients were post-operative. The Sponsor responded that there were 36 normal, healthy subjects who were not post-operative. Since the target patient population of this product is most likely post-operative patients with compromised hemodynamic balance and possibly impaired renal function, the safety database should be based primarily on target patients. Normal, healthy subjects with multiple-dose treatment from PK studies may be counted only if the proportion is small.

The Sponsor stated that 50-75% of use is anticipated for same-day surgery patients and asked if the multiple-dose, one-day treatment could be taken into consideration in determining the safety database requirement. Dr. Hertz noted that the remaining 25-50% of post-operative patients are likely to use the product more than one day and represent a more vulnerable population. Therefore, risk assessment from multiple-dose and multiple-day exposure is required for this product.

The Sponsor stated that they are having difficulty recruiting post-operative patients who will receive Dyloject for the proposed (b) (4) days because doctors will not prescribe parenteral NSAIDs for that duration. Dr. Hertz noted the Sponsor's comment and asked if these patients are still receiving multiple doses on multiple days. The Sponsor responded that they are. Dr. Hertz stated that dosing for at least 2-3 days would be acceptable and the Sponsor must submit a detailed justification to support this change. Dr. Hertz stated that the Division will not press for (b) (4) days if the Sponsor can show that this is not feasible; however, the Division will require the multiple day data for a minimum of 2-3 days.

The Sponsor stated that this product is currently available in the U.K. at 75-mg dosing vs. the proposed 37.5-mg dosing in the U.S.; and the dosing interval in U.K. is 12 hours. The Sponsor asked that, in light of Agency's safety concern with this product's Cmax, whether observational safety data from their open-label study with 75-mg dosing regimen in the U.K. could count towards the safety database requirements.

Dr. Hertz responded that we may consider this open-label safety data if a comparative PK profile between 75 mg and 37.5 mg is supportive.

The Sponsor was planning to conduct single- and multiple-dose PK study in patients with mild renal impairment with a dose of 37.5 mg, and asked if the patients from this study can be counted toward the safety database requirement. Dr. Hertz responded that 20-30 patients from this study could count towards the total safety database requirement and further emphasized that the majority of safety database should be established from post-operative patients.

The Sponsor also planned to conduct an open-label, active-controlled (ketorolac), randomized, safety study in post-operative patients. The patients will be treated with the multiple doses for up to 48 hours. Dosage for patients with high risk factors (such as the elderly) will be reduced to half of the labeled dose, 18.75 mg. The Sponsor asked if these patients could count towards the safety database requirement. Dr. Hertz responded that the Sponsor should provide all potential safety data sources to the Division for review. The Sponsor agreed to do so and asked if they could expect a 30-day turnaround time from the Division. Dr. Hertz stated that she cannot commit to any specific timeline.

### **Clinical:**

#### *Question 12.*

*Javelin is planning to include overviews of efficacy and safety results in sections 2.5.4 (Overview of Efficacy) and 2.5.5 (Overview of Safety); summarized information derived from the full ISE and ISS in sections 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety); and the full set of ISE and ISS documents (text, tables, listings and appendices) in section 5.3.5.3 [Reports of Analyses of Data from More than One Study (Including Any Formal Integrated Analyses, Meta-Analyses, and Bridging Analyses)]. Is this approach acceptable to the Division?*

#### **FDA Response:**

**Yes, it appears acceptable.**

Discussion: No further discussion required.

#### *Question 13.*

*The Statistical Analysis Plans (SAPs) for ISE and ISS are provided in Appendix 5 of the Pre-NDA meeting package. Are the approaches specified in the SAPs for the ISS and ISE acceptable to the Division? (See Appendix 5)*

#### **FDA Response:**

**Yes, it appears acceptable.**

Discussion: No further discussion required.

*Question 14.*

*The pharmacokinetic (PK) characteristics of diclofenac in renal failure are well known, as evidenced by the Agency's findings in the label for Cataflam<sup>®</sup>. DIC075V contains the excipient, hydroxypropyl betadex [hydroxypropyl- $\beta$ -cyclodextrin (HP $\beta$ CD)], whose route of excretion is renal. For this reason, DIC075V will be contraindicated in patients with moderate or severe renal failure.*

*Javelin has enrolled patients with mild degrees of renal failure in its PK study of the elderly and in its Phase 3 efficacy trials. No further PK study in patients with renal failure is planned. Does the Division agree that the planned studies will be sufficient for approval in the absence of a specific PK study in patients with renal failure? (See Appendix 4)*

**FDA Response:**

**No, we do not agree. Although DIC075V will be labeled as contraindicated for patients with moderate and severe renal impairment patients, the pharmacokinetic characteristics of HP $\beta$ CD in patients with mild renal impairment must be assessed with PK studies. The planned studies, DFC-PK-008 and DFC-005, appear insufficient to address the renal safety. Study DFC-PK-008 includes only elderly normal subjects and Study DFC-005 does not specify the subset size of special populations (renal, liver, CV, elderly and GI). This information is necessary to understand potential for renal toxicity associated with both diclofenac and HP $\beta$ CD, particularly given the difference in the target patient population. Post-surgical patients are at risk for fluid shifts and are particularly vulnerable for transient renal insufficiency.**

Discussion:

The Sponsor agreed to conduct specific PK studies in patients with renal impairment in which PK for both diclofenac and HP $\beta$ CD will be determined. The Sponsor stated two study options: 1) a two-group study including normal and mild renal failure patients; 2) a three-group study including normal, mild, and moderate renal failure patients. The Sponsor stated that the sample size of the study is dependent on the breadth of the primary disease state in the population.

Dr. Hertz noted that the Sponsor did contraindicate the moderate to severe renal failure in their proposed package insert and informed the Sponsor that further internal discussion must take place regarding the inclusion of the moderate state, which will be clarified in a post-meeting note.

Dr. Zhang stated that the Sponsor should match age and gender, to the best of their ability, in their defined groups. The Sponsor concurred.

Post-Meeting Note:

The two-arm PK study would be sufficient, but if sufficiently safe to proceed, the three-arm study would be more informative.

*Question 15.*

*Diclofenac is a parenteral NSAID, a class of drugs known to produce gastrointestinal hemorrhage. Patients with moderate to severe liver disease are more liable to gastrointestinal hemorrhage, pancreatitis, and bleeding/clotting abnormalities. For this reason DIC075V will not be recommended in patients with moderate to severe liver disease, although the pharmacokinetics of diclofenac (Cataflam®) have been studied in patients with liver disease.*

*Javelin has enrolled patients with mild degrees of hepatic insufficiency or inflammation in the PK study of obese and elderly patients and in its Phase 3 efficacy trials. Does the Division agree that the planned studies will be sufficient for approval in the absence of a specific PK study in patients with hepatic disease? (See Appendix 4)*

**FDA Response:**

**The planned studies, DFC-PK-008 and DFC-005, appear insufficient to address the hepatic safety. Study DFC-PK-008 includes only elderly normal subjects and the DFC-005 does not specify the subset size of special populations (renal, hepatic, CV, elderly and GI). A specific PK study may not be necessary if additional information from the literature is supportive.**

Discussion:

The Sponsor stated they plan to conduct a specific PK study in patients with liver disease but a PK study may not be adequate to address hepatic safety issues. The Sponsor asked the Division to clarify what population should be studied. Dr. Hertz stated that the Sponsor could contraindicate in populations in which their product is determined to be dangerous. Dr. Hertz clarified that, in such cases, contraindicating means that no further studies would be needed.

The Sponsor stated that, based on case reports, NSAIDS increased GI bleeding in patients with severe liver disease, but patients with mild liver disease could be studied with their product. Moderate to severe liver disease would be contraindicated.

Dr. Hertz stated that, if it is too dangerous to conduct a study in a particular population, the product should be contraindicated in that population. The Sponsor stated that they will take Dr. Hertz's comments under advisement. The Sponsor stated that their product could be studied in patients with mild liver disease and is willing to conduct a study and put subsequent findings into the appropriate labeling sections (ex. WARNINGS and PK). Dr. Hertz informed the Sponsor that even though they can conduct a study, this may not be enough to support use in that population.

*Question 16.*

*No specific risk minimization action plan (RiskMAP) is planned beyond labeling and pharmacovigilance. Is this approach acceptable to the Division?*

**FDA Response:**

**Barring identification of formulation-related safety concerns during the NDA review, risk minimization strategies beyond labeling and pharmacovigilance would not be required for DIC075IV.**

Discussion: No further discussion required.

### **Chemistry, Manufacturing and Controls:**

*Question 17.*

*At the time of NDA filing, Javelin plans to submit stability data through to 6 months* (b) (4)

(b) (4)

(b) (4). *In addition there will be supportive stability data* (b) (4)  
(b) (4) *through to 36 months on 3 pilot scale batches and 18 months on 3 UK validation batches (see Table 1 below). The NDA will also contain a stability commitment to update the stability results as additional data becomes available: i.e., 9, 12, 18, 24 months, etc. (See Appendix 8)*

*Table -1 Stability data to be presented in the NDA at the time of NDA filing*

<i>Manufacturer</i>	<i>Batch Size</i>	<i>Vial size</i>	<i>Stability condition</i>	<i>Stability data</i>
(b) (4)	Three (b) (4) US commercial scale process validation batches		(b) (4)	Through 6 months
				Through 6 months
	Three (b) (4) pilot scale batches			Through 36 months
				Through 6 months
	Three (b) (4) process validation batches for the UK			Through 18 months
				Through 6 months

*Question 17.1*

*Does the Division agree to the proposed stability data in Table-1 that will be presented in the NDA at the time of NDA filing?*

**FDA Response:**

**Yes, this proposal is acceptable. However, we strongly recommend that any amendments of stability data to the NDA, be submitted early in the review cycle. While every effort will be made to review the proposed amendment to the NDA, its review will depend on the timeliness of submission, extent of submitted data and available resources. Therefore, as per GRMP timeliness, we may not be able to review any amendment submitted to the NDA during the review cycle.**

Discussion: No further discussion required.

*Question 17.2*

*Under PDUFA, the Division reviews and acts on standard original NDA submissions within 10 months from the receipt of the NDA. We shall continuously update the NDA with stability data from both (b) (4) batches. Based on the updated stability data (b) (4), we plan to request a shelf life of (b) (4) months. Does the Division agree that a (b) (4)-month shelf life can be granted?*

**FDA Response:**

**The expiration dating will be assessed during review of the NDA. As per ICH Q1E, estimation of the shelf-life will be based on available real time and supporting stability data, observed trends and statistical analysis evaluation.**

Discussion: No further discussion required.

*Question 18.*

*Does the Division agree that the CMC plan included in the pre-NDA information package is sufficient to support and gain NDA approval? (See Appendix 8).*

**FDA Response:**

**The CMC plan is sufficient to support submission of the NDA. Fileability of the NDA and approvability issues will be identified and communicated during the review cycle.**

Discussion: No further discussion required.

**Additional CMC Comments:**

**Provide a complete list of manufacturing facilities with full addresses and verification that they are ready for cGMP inspections in the NDA. For foreign facilities, include a name contact and telephone number at the site.**

**Provide a Pharmaceutical Development Report in the NDA highlighting critical product attributes, formulation development and manufacturing process development. Include manufacturing and control data to support changes during development and demonstrate their impact to drug product quality and performance.**

## **Nonclinical:**

### *Question 19.*

*From the End-of-Phase 2 Division meeting, Javelin was asked to “provide evidence/data which indicates that HP $\beta$ CD does not interfere or trap any other chemical or biological material in the body.” Is the information presented in our submission on 13 September 2007 (serial number 0058) and provided here as Appendix 10 adequate to show that HP $\beta$ CD is not expected to alter the pharmacokinetics of co-administered drugs and endogenous compounds?*

### **FDA Response:**

**We acknowledge your approach taken to address this issue. However, this approach seems overly simplistic. Although, you provided stability constants for complexation for selected drugs, it is unknown what the most ideal stability constants are for drugs to be meaningfully complexed with HP $\beta$ CD. In addition, your assessment in terms of the list of potentially co-administered drugs is limited. Establishing a cutoff for meaningful HP $\beta$ CD complexation of likely coadministered drugs in the intended patient population based on in vitro experiments and the derived stability constants is likely to be more informative. If warranted, in vivo studies may need to be conducted if the stability constants suggest a high likelihood of complexation. Co-medications used in the clinical trials database obtained so far may help in determining the list of co-administered drugs.**

### Discussion:

The Sponsor referenced a list of drugs for evaluation of potential interactions with HP $\beta$ CD, as specified in a White Paper. The Sponsor stated that they found no binding effects greater with HP $\beta$ CD than with plasma proteins.

Dr. Zhang acknowledged the Sponsor’s comment but stated that their model is over-simplified. Dr. Zhang explained that since the binding process is dynamic, the Sponsor should take the PK characteristics of both HP $\beta$ CD and the potentially interacting drugs into consideration and determine the critical constants that could lead to trapping of potential agents.

The Sponsor explained that they can use their PK data to determine the constants in plasma and could then estimate plasma-protein binding with respect to the binding constants of the studied drugs.

Dr. Zhang stated that this was acceptable but the Sponsor will need to provide support for their argument with in vitro bench data or with in vivo data. Dr. Hertz informed the Sponsor that the Division will not include information based on a theoretical concept into the package insert of a drug product. It is necessary for the Sponsor to validate the model they have, based on the protein binding affinities of the drugs, and reflecting on what would actually occur in vivo. Dr. Hertz suggested that the Sponsor study the ability of HP $\beta$ CD to bind something highly protein bound and something loosely protein bound for example, in order to anchor the model. Dr. Hertz explained that the Division is requesting that they validate their model by correlating theory with supporting data.

The Sponsor acknowledged the Division's comments and noted that they will also take into account the clinical concern and relevance when determining which drugs to be studied and designing their supporting studies. The Sponsor asked if the Division would review an updated list of drugs to determine if others should be included. Dr. Hertz responded that they would.

*Question 20.*

*Does the Division agree that the nonclinical plan included in the pre-NDA information package is sufficient to support and gain NDA approval? (See Appendix 7)*

**FDA Response:**

**The nonclinical studies described in the briefing package and referenced in your planned 505(b)(2) submission outline are sufficient to support submission of the NDA. Fileability of the NDA and approvability issues will be identified and communicated during the review cycle.**

**However, before submission of the NDA, in vivo non-clinical data may be needed to adequately assess the potential for drug-drug interactions between diclofenac sodium injection and commonly used drugs to confirm the report provided by the consultant in the briefing package.**

**For the NDA submission, any impurity or degradation product that exceeds ICH thresholds should be adequately qualified for safety as per (ICHQ3A(R), ICHQ3B(R)). Adequate qualification should include:**

- **Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**
- **Repeat dose toxicology of appropriate duration to support the proposed indication.**

Potentially genotoxic impurities or degradation products pose an additional risk; therefore, a specification of NMT (b) (4) mcg/day should be set for genotoxic or potentially genotoxic (b) (4) unless otherwise justified.

Discussion: No further discussion required.

### **Additional Comments: CDISC Data Requests to Sponsors / Quantitative Safety and Pharmacoepidemiology Group**

#### **Safety Analysis Plan**

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, please include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis ([www.cdisc.org](http://www.cdisc.org)).

At a minimum the Safety Analysis Plan should address the following components:

- Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*, <http://www.fda.gov/CDER/guidance/6357fnl.pdf>).
- Safety endpoints for Adverse Events of Special Interest (AERI)
- Definition of Treatment Emergent Adverse Event (TEAE)
- Expert adjudication process (Expert Clinical Committee Charter)
- Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
- Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
- When unanticipated safety issues are identified the QSAP may be amended.

#### **Study Data Tabulation Model (SDTM) Issues**

**1. The current published SDTM and SDTM Implementation Guide (SDTMIG) carefully should be followed.**

- a. Refer to the SDTMIG section on Conformance (3.2.3)**

**2. Domains**

- a. There are additional domains listed below that are not included in the current SDTMIG. Information on these domains may be obtained at [www.CDISC.org](http://www.CDISC.org) and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.**

- i. (DV) Protocol deviations**
- ii. (DA) Drug Accountability**
- iii. (PC, PP) Pharmacokinetics**
- iv. (MB, MS) Microbiology**
- v. (CF) Clinical Findings**

- b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.**

- i. Tumor information**
- ii. Imaging Data**
- iii. Complex Inclusion/Exclusion Criteria**

**3. Variables**

- a. All required variables are to be included.**
- b. All expected variables should be included in all SDTM datasets.**
- c. Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.**
- d. A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.**
- e. A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.**
- f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.**

**4. Specific issues of note:**

- a. SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.**
- b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.**
- c. These issues can be addressed through the request for ADaM datasets**

**Analysis Data Model (ADaM) Issues:**

- 1. Please specify which ADaM datasets you intend to submit.**
- 2. Please include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.**
- 3. Please discuss the structure of the datasets with the reviewing division and specify in the QSAP.**
- 4. Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.**
- 5. Please indicate which core variables will be replicated across the different datasets, if any.**
- 6. SDTM and ADaM datasets should use the unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.**

**General Items:**

- 1. Controlled terminology issues**
  - a. Please use a single version of MedDRA for a submission.**
    - i. Does not have to be most recent version**
  - b. We recommend that the WHO drug dictionary be used for concomitant medications.**
  - c. Please refer to the CDISC terminology for lab test names.**
  - d. Issues regarding ranges for laboratory measurements should be addressed.**

**Additional Comments: Common Physician’s Labeling Rule (PLR) Deficiencies**

**Highlights:**

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4. The drug name must be followed by the drug’s dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement “See full prescribing information for complete boxed warning.” Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line (“margin mark”) on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
7. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

8. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
9. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].
10. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
11. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
12. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
13. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

**Contents (Table of Contents):**

14. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
15. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
16. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
17. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
18. When a subsection is omitted, the numbering does not change. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

- 8.1 Pregnancy
- 8.3 Nursing Mothers (not 8.2)
- 8.4 Pediatric Use (not 8.3)
- 8.5 Geriatric Use (not 8.4)

19. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

**Full Prescribing Information (FPI):**

- 20. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
- 21. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
- 22. Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.
- 23. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not See *Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
- 24. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

- 25. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]**
- 26. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.**
- 27. There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.**
- 28. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.**
- 29. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.**
- 30. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.**
- 31. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.**
- 32. Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.**

**Additional FDA Comments:**

**A. The division requests the following for the submitted datasets:**

- 1. The integrated safety dataset that should include the following fields/variables:**
  - A unique patient identifier
  - Study/protocol number
  - Patient's treatment assignment
  - Demographic characteristics, including gender, chronological age (not date of birth), and race
  - Dosing at time of adverse event
  - Dosing prior to event (if different)
  - Duration of event (or start and stop dates)
  - Days on study drug at time of event
  - Outcome of event (e.g. ongoing, resolved, led to discontinuation)
  - Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
  - Marker for serious adverse events
  - Verbatim term
- 2. The adverse event dataset should include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset should also include the Verbatim term taken from the case report form.**
- 3. Please see the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables should appear and does not address other content that is usually contained in the adverse event data set.**
- 4. In the adverse event data set, please provide a variable that gives the numeric MedDRA code for each lower level term.**
- 5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very**

**helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.**

- 6. Please provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.**
- 7. Please perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, please provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.**
- 8. The spelling and capitalization of MedDRA terms should match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.**
- 9. Also, for the concomitant medication dataset, you should use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.**
- 10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result should be in numeric format.**
- 11. Please perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.**
- 12. In every dataset, all dates should be formatted as ISO date format.**
- 13. Across all datasets, the same coding should be used for common variables, e.g. "PBO" for the placebo group. Datasets should not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable should be included in the datasets.**
- 14. All datasets should contain the following variables/fields (in the same format and coding):**
  - Each subject should have one unique ID across the entire NDA**
  - Study number**

- **Treatment assignment**
  - **Demographic characteristics (age, race, gender, etc.)**
- B. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities.**
- C. For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.**
- D. If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).**

Linked Applications

Sponsor Name

Drug Name

-----  
IND 65048

-----  
JAVELIN  
PHARMACEUTICALS  
INC

-----  
DICLOFENAC SODIUM IV 75MG/2ML

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LAUREN P TORNETTA  
04/08/2008



IND 65,048

Javelin Pharmaceuticals, Inc  
130 W. 42<sup>nd</sup> St, 12<sup>th</sup> Floor  
New York, NY 10036

Attention: Ed Liao  
Director, Clinical Affairs

Dear Mr. Liao:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for injectable diclofenac sodium (DIC075V).

We also refer to the meeting between representatives of your firm and the FDA on April 21, 2006. The purpose of the meeting was to discuss the nonclinical and clinical development plan for DIC075V.

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, call me at (301) 796-1245.

Sincerely,

*{See appended electronic signature page}*

Matthew W. Sullivan  
Regulatory Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

### Industry Meeting Minutes

**Meeting Date:** April 21, 2006 11:00 - 12:30pm

**Location:** White Oak Conference Room 1315

**Drug Name:** Injectable Diclofenac Sodium

**Application:** IND 65,048

**Indication:** Management of acute moderate to severe pain

**Sponsor:** Javelin Pharmaceuticals, Inc.

**Type of Meeting:** End of Phase 2, Type B

**Meeting Chair:** Sharon Hertz, M.D.  
 Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

**Minutes Recorder:** Matthew Sullivan, M.S., Regulatory Project Manager

Javelin Pharmaceuticals, Inc.	Title
Daniel Carr, M.D.	Project Management & Medical Affairs
Curtis Wright, M.D.	Regulatory and Risk Assessment
Michael Moshman	Chemistry, Manufacturing and Controls
Donna Madden	Nonclinical Research
Cynthia Ernst	Clinical Research
Daniel Gawarecki	Biostatistics
(b) (4)	Clinical Research & Regulatory, Consultant
(b) (4)	Pharmacokinetics, Consultant
FDA	Title
Bob Rappaport, M.D.	Director, DAARP
Sharon Hertz, M.D.	Deputy Director, DAARP
Ali Al Hakim, Ph.D.	Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment
Dan Mellon, Ph.D.	Supervisor, Pharmacology/Toxicology, DAARP
Asoke Mukherjee, Ph.D.	Pharmacology/Toxicology Reviewer, DAARP
Joel Schiffenbauer, M.D.	Supervisory Medical Officer, DAARP
Tatiana Oussova, M.D.	Medical Officer, DAARP
Suresh Doddapaneni, Ph.D.	Team Leader, Clinical Pharmacology, DAARP
Yongman Kim, Ph.D.	Statistics Reviewer, DAARP
Dionne Price, Ph.D.	Statistics Reviewer, DAARP
Alex Xu, Ph.D.	Pharmacology/Toxicology Reviewer, DAARP
Matthew Sullivan, M.S.	Regulatory Project Manager, DAARP

**Meeting Objective(s):** Discuss questions related to the nonclinical and clinical development plan for DIC075V.

**Opening Discussion:** Following introductions, the discussion focused on Javelin Pharmaceutical's questions that were included in the March 16, 2006 meeting package. The questions and Division responses are presented below in *italicized* text in the order in which they were addressed at the meeting. Discussion is presented in normal text. The slides containing the Division's responses were sent to the sponsor on April 19, 2006.

*1. Does the Division agree with the data reported and planned for further CMC development to support a NDA submission?*

**FDA response:**

*The development plan for this IND stage is acceptable. However, the following additional CMC issues need to be addressed:*

- 1. For the NDA submission provide a comprehensive Pharmaceutical Development Report. This should contain information on all of the formulations developed for this NDA.*
- 2. The specification limit for the drug product (related impurities and particulate matters) does not reflect the actual stability test data; please revise these limits accordingly.*
- 3. The related substances for diclofenac specification limits are much wider than the USP requirements where impurities total is NMT 0.5%. Please revise these limits as per USP monograph.*
- 4. Stability data should be provided in SAS transport format.*
- 5. Names and addresses for all sites for the drug substance and the drug product involved in manufacturing, testing, packaging, labeling, etc.*
- 6. Provide evidences/data which indicate that Hydroxypropyl- $\beta$ -cyclodextran (HP $\beta$ CD) does not interfere or trap any other chemicals or biological materials in the body.*
- 7. The Pharmaceutical Development Report should also include in-process manufacturing controls based on the experience gained from the NDA batches manufactured for pre-clinical, clinical, pilot and the proposed commercial batches.*
- 8. Follow the recommendations provided in the draft guidance, "Q8 Pharmaceutical Development (Issued 2/7/2005, Posted 2/8/2005)." The guidance can be found on the CDER Web site, <http://www.fda.gov/cder/guidance/6672dft.pdf>*

**Discussion:** With regard to comment number two, the Sponsor inquired as to why the Division was seeking a <sup>(b) (4)</sup> specification limit. The Division replied <sup>(b) (4)</sup>

The Sponsor agreed to do so.

With regard to comment number six, the Sponsor stated that <sup>(b) (4)</sup> there was no evidence that Sporanox

trapped other drugs. Additionally, the Sponsor noted that the marketed Sporanox (itraconazole) product contains (b) (4) HP $\beta$ CD (b) (4)

The Division replied that some standards have changed since Sporanox was approved and that all inactive ingredients must be qualified. The Division noted that there is internal data to suggest that there may be interactions between cyclodextrans and other drugs and endogenous compounds. It is the responsibility of the Sponsor to determine likely co-administered medications and perform an appropriate evaluation for potential drug-drug interactions. Data from clinical trials will not be sufficient to address this given the heterogeneity in concomitant medications and lack of pharmacologic data. Literature references alone are unlikely to provide adequate data for this product.

The Sponsor agreed to provide qualification data for their inactive ingredients.

*2. Does the Division agree that the PK studies completed in addition to a multiple dose PK study (DFC-PK-005) will be sufficient for an NDA filing?*

**FDA response:**

- 1. For a 505 (b)(2) application, information on the bioavailability of your drug product relative to a listed drug in the Orange Book is required.*
- 2. Related to HP $\beta$ CD, the following information should be adequately addressed;*
  - a. in vivo fate*
  - b. safety in renal impairment subjects due to potential accumulation*
  - c. potential to affect disposition of concomitant drugs*

**Discussion:** The Sponsor asked whether or not it was acceptable to use Cataflam (diclofenac potassium) as the reference listed product, even though their product uses the sodium salt. The Sponsor noted that there aren't any immediate-release diclofenac sodium products listed in the orange book. The Division agreed that Cataflam may be a more reasonable product to use as the reference listed product rather than a modified-release diclofenac sodium product.

Additionally, the Sponsor commented that they will be relying on the literature for much of this required data including data on renal excretion in renal insufficiency. The Division explained to the Sponsor that it will be necessary to have quantitative information about accumulation in renal insufficiency. The Sponsor noted that with Sporanox, the half-life doubled in severe renal insufficiency and, therefore, this would be a contraindication for the product. Patients with serum creatinine levels up to 2 will be included in the clinical trials.

The Sponsor alerted the Division that their pre-clinical plan would be forthcoming.

**Post-Meeting Note:** The Division confirms that it is appropriate for the Sponsor to list Cataflam (diclofenac potassium) as the reference listed drug product.

3. Does the Division agree that the proposed clinical studies will satisfy the division's safety population for NDA filing?

**FDA response:**

*No. An adequate number of patients exposed to multiple dosing for an adequate period of time will be necessary. A definitive requirement for the safety database cannot be determined prior to demonstration of the relative bioavailability to a product approved in the U.S. If the PK profile of your product does not exceed the  $C_{max}$  or AUC of the reference listed product, a minimum of 500 patients exposed to multiple doses over multiple days of the to-be-marketed formulation of diclofenac must be included in the safety database. This is due to the novel route of administration, the post-operative population which is at greater risk for renal toxicity in the setting of fluctuations in fluid balance, the potential for additive or synergistic renal toxicity for diclofenac in combination with the  $\beta$ -cyclodextran, and the potential for additive or synergistic hepatic toxicity for diclofenac in combination with the  $\beta$ -cyclodextran. If the relative bioavailability of your product exceeds the reference listed product by  $C_{max}$  or AUC, additional safety data will be necessary. It will also be necessary to study hepatic and renal impaired patients and elderly patients (above the age 65). In addition to following renal and hepatic function, it will be necessary to collect information on any possible negative effects on wound healing. Clinical studies must permit (but do not need to require) up to 5 days of dosing in those patients not yet converted to oral analgesics, in order to collect as much safety data as possible.*

**Discussion:** The Sponsor indicated that the  $C_{max}$  of the reference listed product will be exceeded, and wondered how many patients would be required for their safety database. The Division replied that a minimum database of 1000 patients would be required. The Sponsor commented that in order to enroll a sufficient numbers of patients, they would likely need to expand the inclusion criteria to allow additional patients to be included, for example, those up to 80 years of age and those with renal impairment and liver impairment. The Division replied that this was acceptable.

The Sponsor commented that they would likely be enrolling a large number of patients over the age of 50 in their Phase 3 trials, even though they were unsure whether this age group would make up much of the intended population for the marketed product. The Division replied that this was acceptable.

The Sponsor inquired about recording wound healing as an adverse event. They indicated that these adverse events usually occur within seven days of drug injection, well within the 30-day study observation period. The Division concurred with this plan.

The Sponsor stated that they planned to only dose patients for two days post surgery. They plan to limit use for no more than 48 hours based on European data. The patients would then be converted to oral medication. The Division replied that they would like data out to five days if possible, because there will be a spectrum of actual use with the approved product, likely including use for more than two days as an inpatient medication. It is important to know if it is unsafe for use longer than two days. The Sponsor agreed to provide data for all usage after two days, even if it is only in a minority of patients. The Division agreed that the primary efficacy endpoint could be on Day 2 as long as safety data is collected for as long as patients use the product.

With regard to oral analgesic use after discharge, the Sponsor expressed concern about possible acetaminophen associated hepatic toxicity and about cumulative toxicity with an oral NSAID. The Division noted that it would be extremely important to capture data on post-discharge analgesic use, especially whether an NSAID was used. The Sponsor commented that there was no expectation of additional hepatotoxicity with the parenteral formulation as hepatotoxicity with the oral products appears to be related to cumulative dose and duration of exposure.

*3.a. Does the Division agree with the proposed primary and secondary endpoints in the proposed clinical study?*

**FDA response:**

*Summary of pain intensity (SPID) is an acceptable primary endpoint, but the time period used for the analysis must include an evaluation through day three. In addition, metrics such as time to onset of analgesia and time to re-medication must be evaluated to support the indication and the dosing regimen in a clinically relevant patient population. We are concerned that the dosing interval identified in dental pain studies may not be the same for post-operative pain. The proposed secondary endpoints appear appropriate.*

*Also, in principle, missing data due to adverse event or inadequate pain relief should not be imputed with good scores in calculation of SPID. Use of the 6 hour time window in the proposed worst observation carried forward seems to violate the principle.*

**Discussion:** The Sponsor inquired if a Day 2 efficacy assessment is acceptable for a two-day drug. The Division replied that they would like at least three days of data (and ideally five days), but that using Day 2 as the primary endpoint, and day 3 as a secondary endpoint would be acceptable. The Sponsor commented that they planned to assess time to onset and to re-medication. The Division noted that the double stopwatch method is the most reliable and that there was currently no known correlation between the Sponsor's method and pain relief scores. If both were collected, the Sponsor could attempt to validate the latter.

The Division clarified that baseline observation carried forward (BOCF) would be not be acceptable for those patients who withdrew due to inadequate pain relief or adverse event. The use of the six-hour time window is appropriate.

*4. Does the Division agree it is appropriate to include patients administered DIC075T and DIC075U in the safety population?*

**FDA response:**

*Inclusion of these patients into the ISS is appropriate and would enhance our understanding of this drug's safety profile. However, please provide an analysis of safety for these formulations separate from your proposed formulation for registration.*

**Discussion:** There was no additional discussion beyond the information presented in the slides.

4.a. Does the Division agree that the proposed safety population of approximately 800 patients is sufficient for NDA filing?

**FDA response:**

See our answer to question 3.

*In addition, we would need to see a robust assessment of possible adverse events (AEs) that might occur after patients were discharged home. Out-patient follow up assessment of AEs needs to continue for 4 weeks after the last dose.*

*Describe how pain will be managed following discontinuation of parenteral therapy with study drugs. Will patients be permitted to continue on oral diclofenac?*

**Discussion:** The Sponsor reiterated their earlier comment that they would follow 1000 patients for four weeks after the last dose.

5. Does the Division agree that the completed DFC-001 & DFC-002 dental studies and proposed DFC-004 abdominal study, if successful, are adequate to support the proposed indication of “acute moderate to severe pain”?

**FDA response:**

*No. Single-dose efficacy studies do not support efficacy when multiple-dose treatment will be anticipated. Replicated multiple-dose studies would be required. In addition to abdominal surgery model, we strongly encourage you to explore a different pain model (such as bone pain after hip replacement surgery), to obtain additional safety as well as efficacy in another population.*

**Discussion:** The Sponsor agreed to investigate and pursue hip and knee replacement surgery. Additionally, they commented that they believed single-dose data would be very useful since the marketed product will likely get used in this manner.

6. Does the Division agree that pediatric trials will not be required for NDA filing due to the safety risks likely from such usage?

**FDA response:**

*Pediatric studies are not required at the time of NDA filing. The deferral of pediatric studies at this time would be appropriate until the risk-benefit profile of the drug is better understood from studies in adults. If you desire a partial waiver for pediatric population of a certain age, justification for this should be provided.*

**Discussion:** There was no additional discussion beyond the information presented in the slides.

7. Does the Division agree that the completed nonclinical studies conducted to date support a NDA filing?

**FDA response:**

*The nonclinical studies completed to date with the proposed clinical formulation (full battery of genetic toxicology studies and 4-week intravenous repeat-dose toxicology studies in the rat and monkey model) may be used to support filing of your 505(b)(2) NDA application.*

*Your NDA application should summarize and evaluate safety of the drug substance and excipients. Please provide copies of all references that support the safety of the components of the drug product with the NDA.*

*Information with respect to mutagenicity, carcinogenicity, and reproductive toxicology data on diclofenac may be referenced as part of a 505(b)(2) application, assuming adequate patent certification is provided. The following comments are from the October 1999 DRAFT Guidance for Industry: Applications Covered by Section 505(b)(2), available at <http://www.fda.gov/cder/guidance/guidance.htm>:*

- 1. 505(b)(2) applications must clearly identify those portions of the application that rely on information you do not own or to which you do not have a right of reference.*
- 2. A 505(b)(2) application that relies upon the Agency's previous finding of safety or efficacy for a listed drug must specifically identify any and all listed drugs by established name, proprietary name, dosage form, strength, route of administration, name of the listed drug's sponsor and the application number.*
- 3. A 505(b)(2) application relying upon literature must clearly identify the listed drug(s) on which the studies were conducted (if any).*
- 4. For a 505(b)(2) application you must provide a patent certification or statement as required under section 505(b)(2) of the Act with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug (21 CFR 314.54(a)(1)(vi)). -- (Listed in the Orange Book)*
- 5. Patent certification should specify the exact patent number(s), and the exact name of the listed drug or other drug even if all relevant patents have expired.*
- 6. Note the following key issue regarding the requirement for appropriate patent certification: Due to legislation contained in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), if during the review of an NDA filed under 505(b)(2), either the applicant decides to refer to a different product than that/those identified in the original application, or the Agency discovers that the applicant did not appropriately certify to the patent(s) of the products referenced in the original application, then the applicant*

*would be required to withdraw and resubmit the application as a new original NDA, with the appropriate Patent Certifications included, potentially requiring a new User Fee.*

- 7. Before submitting your NDA, the guidance recommends that you submit a plan to the reviewing Division that specifically identifies the types of bridging studies that will be conducted. You should also identify those components of its application for which you expect to rely on FDA's finding of safety and effectiveness of a previously approved drug product. The Division will critique the plan and provide guidance.*
- 8. The review of this plan will be completed around Division deadlines that may take higher priority; therefore, the Division encourages that you submit such a plan well in advance of the NDA submission, to provide adequate time for the reviewer to evaluate the proposal and resolve any potential concerns that may result in a filing issue or delay in the review process.*
- 9. You must also submit a relative bioavailability study comparing the proposed product to the listed drug(s) (if any).*
- 10. If the only literature that you submit is within the public domain and/or you have right of reference to the studies and the data required to support them, you may be able to submit a 505(b)(1) application.*
- 11. If portions of your application rely upon studies that you do not have right of reference to or are not within the public domain, you must submit a 505(b)(2) application. Please note that not all studies reported in the literature are supported by data that exists within the public domain. Many studies in the literature are supported by proprietary data.*
- 12. For the NDA, you may need to complete nonclinical pharmacokinetic bridging studies in order to compare exposures obtained in the referenced drug product with those obtained with your drug product for the product labeling.*

**Discussion:** With regard to comment number 12, the Sponsor requested clarification as to whether or not an IV to PO bridging pharmacokinetic study would be required. They commented that they would be comparing a product with 100% bioavailability to a product with approximately 50% bioavailability. The Division replied that a side-by-side comparison would be needed so that we could compare the pharmacokinetic profiles and assess potential differences in clinical effects, should there be any. The Sponsor commented that the  $C_{max}$  for their product is expected to be significantly higher and a head to head study is not needed to confirm it.

The Division commented that because there are different  $C_{max}$  values between the reference listed drug and the proposed drug, the Sponsor should ensure that adequate preclinical coverage is available to cover all doses.

Additionally, the Sponsor agreed to provide data from the European experience with IV Diclofenac.

**Post-Meeting Note:** A head-to-head relative bioavailability study comparing IV diclofenac sodium

and an oral reference listed drug product is not required based on the provided rationale.

**Action Items:**

None

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/s/

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Matthew Sullivan

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