

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022396Orig1s000

CHEMISTRY REVIEW(S)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

App on: NDA 22396/000
Stamp Date:
Regulatory:

Action Goal:
District Goal: 04-AUG-2010

Applicant: HOSPIRA INC
125 CAMBRIDGE PARK DR
CAMBRIDGE, MA 02140

Brand Name: DIC075V
Estab. Name:
Generic Name:

Priority: 3
Org. Code: 170

Product Number; Dosage Form; Ingredient; Strengths
001; INJECTION; DICLOFENAC SODIUM; 37.5MG/1ML

Application: NDA 22396/000
Stamp Date: 03-DEC-2009
Regulatory: 03-OCT-2010

Action Goal:
District Goal: 04-AUG-2010

Applicant: HOSPIRA INC
125 CAMBRIDGE PARK DR
CAMBRIDGE, MA 02140

Brand Name: DIC075V
Estab. Name:
Generic Name:

Priority: 3
Org. Code: 170

Product Number; Dosage Form; Ingredient; Strengths
001; INJECTION; DICLOFENAC SODIUM; 37.5MG/1ML

Application Comment: THIS IS A 505(B)2 APPLICATION. THE REFERENCE LISTED DRUG IS CATAFLAM (SPONSOR: NOVARTIS) (on 14-DEC-2009 by D. HENRY () 301-796-4227)

THE CONTACT PERSON FOR THE APPLICATION IS ROBERTA TUCKER, PHONE: 617-349-4500 (on 14-DEC-2009 by D. HENRY () 301-796-4227)

THE IS APPLICATION HAS BEEN ASSIGNED A STANDARD REVIEW. THE GOAL DATE IS OCT 3, 2010 (on 22-JAN-2010 by D. HENRY () 301-796-4227)

FDA Contacts:	D. HENRY	Project Manager	301-796-4227
	M. HABER	Review Chemist	301-796-1675
	D. CHRISTODOULOU	Team Leader	301-796-1342

Overall Recommendation: ACCEPTABLE on 29-SEP-2010 by E. JOHNSON (HFD-320) 301-796-3334

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

- Responsibilities:**
- FINISHED DOSAGE LABELER
 - FINISHED DOSAGE MANUFACTURER
 - FINISHED DOSAGE PACKAGER
 - FINISHED DOSAGE RELEASE TESTER
 - FINISHED DOSAGE STABILITY TESTER

Estab. Comment: MANUFACTURES AND PACKAGES THE DRUG PRODUCT, DYLOJECT (DICLOFENAC SODIUM) INJECTION, 37.5 MG/ML, IN 1 ML (b) (4) FILLS, AND IS RESPONSIBLE FOR QUALITY CONTROL OF THE STARTING MATERIALS AND FINISHED PRODUCT. (b) (4) ALSO CONDUCTS THE STABILITY STUDIES FOR DYLOJECT. (on 14-DEC-2009 by D. HENRY () 301-796-4227)

Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-DEC-2009				HENRYD
SUBMITTED TO DO	18-DEC-2009	10-Day Letter			INYARDA
INSPECTION SCHEDULED	24-FEB-2010		19-MAR-2010		KDOBILAS
AS. ED INSPECTION TO IB	24-FEB-2010	Product Specific			KDOBILAS
DO RECOMMENDATION	16-MAR-2010			ACCEPTABLE	KDOBILAS
GMP & PAI INSPECTION OCCURRED	(b) (4)	NAI. PROFILE IS ACCEPTABLE.		INSPECTION	
OC RECOMMENDATION	16-MAR-2010			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)

DMF No: [REDACTED] (b) (4)

AADA:

Responsibilities: DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
INTERMEDIATE MANUFACTURER

Establishment Comment: PER EMAIL FROM M. HABER 9/13/10: THIS API MANUFACTURER [REDACTED] (b) (4) MAKES WHAT IT CALLS [REDACTED] (b) (4) THE DRUG SUBSTANCE [REDACTED] (b) (4) THE NDA WAS REVIEWED BY MICROBIOLOGY REGARDING STERILIZATION AND THE REVIEW IS IN DARRTS THAT THE STERILIZATION PROCESS IS ADEQUATE. (on 13-SEP-2010 by A. INYARD ()) BULK DRUG SUBSTANCE, DICLOFENAC SODIUM USP, IS MANUFACTURED, TESTED, AND PACKAGED [REDACTED] (b) (4) (on 14-DEC-2009 by D. HENRY () 301-796-4227)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-DEC-2009				HENRYD
SUBMITTED TO DO	18-DEC-2009	GMP Inspection			INYARDA
ASSIGNED INSPECTION TO IB	15-JAN-2010	GMP Inspection			JOHNSONE
DC RECOMMENDATION	29-SEP-2010			ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	29-SEP-2010			ACCEPTABLE DISTRICT RECOMMENDATION	PHILPYE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Estab. ment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Estab. Comment: (b) (4)
THE NEW DMF (b) (4) DESCRIBES THE MANUFACTURING PROCESS. (on 11-JAN-2010 by M. HABER () 301-796-1675)

(b) (4)
(on 14-DEC-2009 by D. HENRY () 301-796-4227)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-DEC-2009				HENRYD
SUBMITTED TO DO	18-DEC-2009	GMP Inspection			INYARDA
ASSIGNED INSPECTION TO IB	15-JAN-2010	GMP Inspection			JOHNSONE
DO RECOMMENDATION	29-SEP-2010			ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	29-SEP-2010			ACCEPTABLE DISTRICT RECOMMENDATION	PHILPYE

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/s/

MARY GRACE LUBAO
01/07/2015



Public Health Service

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Memorandum

Date: December 18, 2014

To: DARRTS and Panorama

From: Julia Pinto, Ph.D.

Subject: CMC Memo to File Regarding NDA 22396
Dyloject (Diclofenac Sodium) Injection

Applicant: Javelin Pharmaceuticals (Subsidiary of Hospira Inc.)
275 North Field Drive, Lake Forest, IL 60045

Product: Dyloject (Diclofenac Sodium) Injection

Indication: For the management of acute pain in adults. The dosage is 37.5mg (1 mL) administered by intravenous bolus injection.

Presentations: 2 mL glass vial with 1 mL of solution containing 37.5 mg/mL.
The vial is for single use only (b) (4) The secondary packaging consists of a white cardboard carton holding 25 vials.

Javelin Pharmaceuticals Inc. originally submitted this NDA 22396 on 3-Dec-2009 for their drug product diclofenac sodium injection. (b) (4)
(b) (4) Office of Compliance recommended a withhold recommendation for the manufacturing facility and hence a Complete Response action was taken for the NDA.

Javelin submitted a complete response to the NDA on June 28th, 2013, to address the withhold issues cited by OC. Javelin and their contract manufacturer (b) (4) indicated that they had addressed all inspection related issues as they had responded to the 483 observations. However, Dr. Juandria Williams Ph.D. from the Office of Manufacturing and Product Quality in a review memo dated 17-DEC-2013

(Filed in DARRTS) made a recommendation that the application should not be approved due to continued GMP issues for the (b) (4) site that manufactures and tests the drug product. Therefore, a continued overall withhold recommendation was made for the NDA on Dec 16th 2013.

In the current Submission, dated October 31, 2014, Javelin again, submits a complete response to the NDA, to address the inspection issue (b) (4) at the (b) (4) Facility (a contract manufacturer).

Dr. Juandria Williams, Ph.D. from the Office of Manufacturing and Product Quality in a review memo dated 18-DEC-2014 (Filed in Panorama), has made a recommendation that the application be approved since all issues (b) (4) at that (b) (4) Facility have been resolved. The Office of Compliance has provided an overall acceptable recommendation for all facilities (attached below).

Conclusion: Therefore since all outstanding inspection issues have been adequately resolved, and no additional CMC changes have been submitted, this NDA is recommended for approval, from the CMC perspective.

Julia C. Pinto, Ph.D.
Acting Branch Chief, Branch VIII
ONDQA

(b) (4)

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/s/

JULIA C PINTO
12/19/2014



Dyloject (diclofenac sodium) Injection NDA 22-396

DATE: Dec. 18, 2013
TO: DARRTS
FROM: Prasad Peri, Ph.D,
SUBJECT: CMC Secondary Review of Dyloject NDA 22396 (**Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls**)

Applicant: Hospira, Inc. (formerly Javelin Pharmaceuticals).
275 North Field Drive, Lake Forest, IL 60045

Product: Diclofenac Injection

Indication: For the management of acute pain in adults. The dosage is 37.5 mg (1 mL) administered by intravenous bolus injection.

Presentations: 2 mL glass vial with 1 mL of solution containing 37.5 mg/mL. Treatment may be repeated every 6 hours, not to exceed 150 mg/day. The vial is for single use only [REDACTED] (b) (4). The secondary packaging consists of a white cardboard carton holding 25 vials.

Javelin Pharmaceuticals Inc. originally submitted an NDA on 3-Dec-2009 for their drug product diclofenac sodium injection. [REDACTED] (b) (4)

[REDACTED] Office of Compliance recommended a withhold recommendation for the manufacturing facility and hence a Complete Response action was taken for the NDA.

In this current submission, Hospira Inc. (the new owner of the NDA) submitted a complete response to the NDA on June 28th 2013. [REDACTED] (b) (4)

[REDACTED] (b) (4)

In addition, Hospira and their contract manufacturer [REDACTED] (b) (4) indicated that they had addressed all inspection related issues as they had responded to the 483 observations.



Dyloject (diclofenac sodium) Injection

NDA 22-396

Dr. Juandria Williams Ph.D. from the Office of Manufacturing and Product Quality in a review memo dated 17-DEC-2013 has made a recommendation that the application should not be approved due to continued GMP issues for the (b) (4) site that manufactures and tests the drug product.

An overall **withhold recommendation** has been made for the NDA on Dec 16th 2013.

ONDQA Conclusion: The CMC team recommends a **complete response** for the NDA until a final acceptable recommendation from the Office of Compliance for all manufacturing and testing facilities.

Prasad Peri Ph.D.
Branch Chief, Branch VIII
ONDQA.



Dyloject (diclofenac sodium) Injection

NDA 22-396

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Application: NDA 22396/000 **Action Goal:**

Stamp Date: 03-DEC-2009 **District Goal:** 29-OCT-2013

Regulatory: 28-DEC-2013

Applicant: JAVELIN PHARMS INC **Brand Name:** DIC075V
275 NORTH FIELD DR DEPT 0392 BLDG H2 2 **Estab. Name:**
LAKE FOREST, IL 60045 **Generic Name:**

Priority: 3 **Product Number; Dosage Form; Ingredient; Strengths**

Org. Code: 170 001; INJECTION; DICLOFENAC SODIUM; 37.5MG/1ML

Application Comment: THIS IS A 505(B)2 APPLICATION. THE REFERENCE LISTED DRUG IS CATAFLAM (SPONSOR: NOVARTIS) (on 14-DEC-2009 by D. HENRY () 3017964227)
THE CONTACT PERSON FOR THE APPLICATION IS ROBERTA TUCKER, PHONE: 617-349-4500 (on 14-DEC-2009 by D. HENRY () 3017964227)
THE IS APPLICATION HAS BEEN ASSIGNED A STANDARD REVIEW. THE GOAL DATE IS OCT 3, 2010 (on 22-JAN-2010 by D. HENRY () 3017964227)

FDA Contacts:

M. HABER	Prod Qual Reviewer		3017961675
D. HENRY	Product Quality PM		3017964227
S. PATWARDHAN	Regulatory Project Mgr	(HF-01)	3017964085
D. CHRISTODOULOU	Team Leader		3017961342

Overall Recommendation:	WITHHOLD	on 16-DEC-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 02-JUL-2013	by EES_PROD		
	PENDING	on 02-JUL-2013	by EES_PROD		
	WITHHOLD	on 21-DEC-2010	by C. CRUZ	(HFD-323)	3017963254
	ACCEPTABLE	on 29-SEP-2010	by E. PHILPY	(HFD-325)	3017963334

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/s/

PRASAD PERI
12/19/2013
CR recommendation



Dyloject (diclofenac sodium) Injection NDA 22-396

DATE: Dec 3, 2013
TO: DARRTS
FROM: Prasad Peri, Ph.D,
SUBJECT: CMC Secondary Review of Dyloject NDA 22396 **Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls**

Applicant: Hospira, Inc. (formerly Javelin Pharmaceuticals).
275 North Field Drive, Lake Forest, IL 60045

Indication: For the management of acute pain in adults. The dosage is 37.5 mg (1 mL) administered by intravenous bolus injection.

Presentations: 2 mL glass vial with 1 mL of solution containing 37.5 mg/mL. Treatment may be repeated every 6 hours, not to exceed 150 mg/day. The vial is for single use only. (b) (4) The secondary packaging consists of a white cardboard carton holding 25 vials.

Javelin Pharmaceuticals Inc. originally submitted an NDA on 3-Dec-2009 for their drug product diclofenac sodium injection. (b) (4)

(b) (4) Office of Compliance recommended a withhold recommendation for the manufacturing facility and hence a Complete Response action was taken for the NDA.

In this current submission, Hospira Inc. (the new owner of the NDA) submitted a complete response to the NDA on June 28th 2013. (b) (4)

(b) (4)
In addition, Hospira and their contract manufacturer (b) (4) indicated that they had addressed all inspection related issues as they had responded to the 483 observations.

The drug product manufacturing facility has undergone an inspection and a final recommendation from the office of compliance is pending.



Dyloject (diclofenac sodium) Injection

NDA 22-396

Conclusion: The CMC team recommends approval of the NDA pending a final acceptable recommendation from the Office of Compliance for all manufacturing and testing facilities.

Prasad Peri
Branch Chief,
ONDQA.

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/s/

PRASAD PERI
12/04/2013

NDA 22-396

Dyloject (diclofenac Sodium) Injection

Memo to File

Applicant: Hospira, Inc.

Presentation: The drug product is presented in a 1 mL fill volume in a 2 mL size clear glass vial with a 13 mm (b)(4) rubber stopper and aluminum overseal.

EER Status: AC with p-OAI Alert

Environmental Assessment Consult: EA review in DARRTS by Dr. E. McVey dated 9/13/2010 recommends FONSI for this application.

The previous addendum to Chemistry Review #1, finalized 9/24/2010, incorrectly stated that the (b)(4) drug product manufacturing site was not inspected for this NDA by the district office and was found acceptable based on profile as of 3/16/2010. In fact, there was a pre-approval inspection performed at the (b)(4) facility (b)(4) along with a surveillance inspection and coverage of two other applications (an sNDA and an ANDA). An approval recommendation was provided (b)(4) on 3/16/2010 by the district office. An overall acceptable recommendation for all EES sites was made on 9/29/2010.

As discussed in the previous Addendum, (b)(4) the review division and ONDQA are recommending a "For Cause Inspection" of the drug product manufacturer's facility (b)(4). The Office of Compliance, the Office of New Drug Chemistry and the (b)(4) District Office are preparing for a limited pre-approval inspection (b)(4)

(b)(4)

Until an additional for-cause inspection is performed and a further satisfactory recommendation issued for all manufacturing sites by the Office of Compliance, the NDA is recommended for a complete response.

Martin Haber, Ph.D.
Chemistry Reviewer, DNDPAIII/ONDQA

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/s/

MARTIN T HABER
10/01/2010

PRASAD PERI
10/01/2010
I concur

Dyloject (diclofenac sodium) Injection

NDA 22-396

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Hospira, Inc. (formerly Javelin Pharmaceuticals).
275 North Field Drive, Lake Forest, IL 60045

Indication: For the management of acute pain in adults. The dosage is 37.5 mg (1 mL) administered by intravenous bolus injection.

Presentations: 2 mL glass vial with 1 mL of solution containing 37.5 mg/mL. Treatment may be repeated every 6 hours, not to exceed 150 mg/day. The vial is for single use only (b) (4). The secondary packaging consists of a white cardboard carton holding 25 vials.

EER Status: Acceptable as of Sept. 29, 2010.

Consults: **EA** – Categorical exclusion not granted due to recent scientific articles that seem to indicate toxic effects of diclofenac to fish. An environment assessment was prepared by Javelin and was found acceptable by OPS staff Emily McVey.
Methods Validation – Revalidation by Agency will not be requested since the methods listed are standard.
Pharmacology/Toxicology – Acceptable, all impurities have been qualified.
Biopharmaceutics – N/A.
Quality Microbiology – Acceptable.

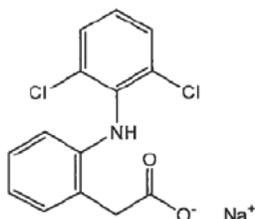
Original Submission: 24-Sep-2009

Post-Approval CMC Commitments:

(b) (4)

Drug Substance:

The drug substance, diclofenac sodium, was first approved in the 1970's and is the subject of a USP monograph. There are several previously approved formulations for both the sodium and potassium salt forms. The diclofenac molecule is a weak acid with no chiral centers. The sodium salt is used for this NDA.



MOLECULAR FORMULA: C₁₄H₁₀Cl₂NNaO₂

MOLECULAR WEIGHT: 318.13

The bulk drug substance is manufactured by (b) (4) CMC information for the (b) (4) site is provided in DMF (b) (4) which was reviewed on 8/11/10 and found adequate. Facility inspection is pending for this site. Originally the applicant had proposed a second site (b) (4). This site was withdrawn from the application.

The NDA provides little information regarding drug substance manufacturing and cross-references all information to DMF (b) (4). The drug substance is tested to be in compliance with the USP monograph. In addition to USP tests, bioburden and bacterial endotoxins tests are added to qualify the use of the drug substance as a component suitable for parenteral use. USP tests include description, identification, assay, chromatographic purity, color of solution, clarity of solution, solution pH, loss on drying, and heavy metals. The NDA sponsor states that likely impurities include (b) (4). They state however that typically no (b) (4) or any other impurity is observed by the validated HPLC method with a limit of detection of (b) (4)%. The specification limits for (b) (4) any individual unknown related substance were (b) (4)% as requested by the Agency in accordance with the ICH Q3A guideline.

Based on the data collected (b) (4) assigns a (b) (4) retest date to lots of drug substance stored (b) (4). The drug substance is stored (b) (4).

Conclusion: The drug substance is satisfactory pending inspection of manufacturing site.

Drug Product:

The drug product is an aqueous solution (1 mL) presented in a 2 mL USP Type I flint glass vial with a 13 mm (b) (4) rubber stopper and aluminum overseal. The secondary packaging consists of a white cardboard carton holding 25 vials. The concentration of the active is 3.75%, resulting in a strength of 37.5 mg of diclofenac sodium in 1 mL. (b) (4)

The drug product is manufactured (b) (4). The facility cGMP status for this site only was acceptable based on the district recommendation as of 3/16/2010.

The drug product vial contains the following excipients: 333^{(b) (4)} mg hydroxypropyl-beta-dex (β -cyclodextran), 5.0 mg monothioglycerol, and traces of hydrochloric acid/sodium hydroxide added to adjust the pH ^{(b) (4)}

The manufacturing process involves ^{(b) (4)}

The release specifications include tests for appearance, identification, color, pH, osmolality, volume in container, hydroxypropyl beta-dex assay, monothioglycerol assay, assay (diclofenac sodium), related substances ^{(b) (4)} individual unknowns, total unknowns, particulate matter, sterility, bacterial endotoxins and container-closure integrity.

Stability studies showed ^{(b) (4)} . The assay results ^{(b) (4)} ranged from ^{(b) (4)}%. Test results for all parameters remained within proposed acceptance limits for 18 months at room temperature. The expiry dating period is determined to be **18 months** for the drug product.

^{(b) (4)}
The drug product was found acceptable based on the data provided in the NDA, however there are other issues ^{(b) (4)}

^{(b) (4)}

^{(b) (4)}

^{(b) (4)}

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Note that this data is provided in the penultimate week of the PDUFA goal date (Oct. 3, 2010). The investigation results will need further evaluation by the Office of New Drug Quality Assessment, the Office of Compliance, Division of Manufacturing and Product Quality and the District Office for the site. It will also require an on-site inspection to verify that the investigation was adequate and that appropriate changes have been correctly implemented. (b) (4)

The (b) (4) site was not inspected for this NDA by the district office and was found acceptable based on profile as of 3/16/2010.

Thus based on the evaluation of the recently available data, a “For Cause” inspection should be conducted of the applicant’s contract manufacturing facility (b) (4) to assure that the facility fully complies with current Good Manufacturing Practices prior to the approval of the current NDA.

The clinical division has decided that as there will not be adequate time to complete all this work before the PDUFA date of 10/3/2010, the best regulatory action under the current circumstances is a Complete Response. The CMC team agrees with the clinical division and that the recommendation should be a complete response. The possible draft comment for the action letter is stated below.

Conclusion: (b) (4)

Office of compliance will need to perform an inspection of the applicant’s drug product manufacturing facility (For Cause Inspection) and evaluate the proposed corrective actions. Hence it is recommended that the application be not approved from a CMC perspective.

Outstanding issues: For Cause Inspection of the drug product manufacturing facility (b) (4)

Additional Items:

Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Method validation will not be requested since all methods are standard.

Overall Conclusion:

From a CMC perspective, the application is recommended for a complete response and a For Cause Inspection of the drug product manufacturing and testing facility (b) (4) is recommended.

Draft Language for Complete Response Letter is shown below.

(b) (4)

(b) (4)

Based on the currently available data provided in the amendment dated September 23, 2010, we are recommending a “For Cause Inspection” of the drug product manufacturer’s facility (b) (4)

(b) (4)

An inspection must be performed and a satisfactory recommendation issued for all manufacturing sites by the Office of Compliance prior to marketing of this product.

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/s/

PRASAD PERI

09/30/2010

recommend CR and a for cause inspection

NDA 22-396

Dyloject (diclofenac Sodium) Injection

Addendum to Chemistry Review #1

Applicant: Hospira, Inc.

Presentation: The drug product is presented in a 1 mL fill volume in a 2 mL size clear glass vial with a 13 mm ^{(b) (4)} rubber stopper and aluminum overseal.

EER Status: Pending

Environmental Assessment Consult: EA review in DARRTS by Dr. E. McVey dated 9/13/2010 recommends FONSI for this application.

Background:

The previous review for chemistry, manufacturing and controls by Dr. M. Haber dated 9/2/2010 recommended approval pending an acceptable overall manufacturing facilities evaluation and an EA FONSI. ^{(b) (4)}

^{(b) (4)}

^{(b) (4)}

Evaluation: Inadequate

Note that this data is provided in the penultimate week of the PDUFA goal date (Oct. 3, 2010). The investigation results will need further evaluation by the Office of New Drug Quality Assessment, the Office of Compliance, Division of Manufacturing and Product Quality and the District Office for the site. It will also require an on-site inspection to verify that the investigation was adequate and that appropriate changes have been correctly implemented. (b) (4)

The (b) (4) site was not inspected for this NDA by the district office and was found acceptable based on profile as of 3/16/2010. No information has been provided as to when the (b) (4) facility will be found acceptable (b) (4)

Thus based on the evaluation of the recently available data, a “For Cause” inspection should be conducted of the applicant’s contract manufacturing facility (b) (4) to assure that the facility fully complies with current Good Manufacturing Practices prior to the approval of the current NDA.

The clinical division has decided that as there will not be adequate time to complete all this work before the PDUFA date of 10/3/2010, the best regulatory action under the current circumstances is a Complete Response. The CMC team agrees with the clinical division and that the recommendation should be a complete response. The possible draft comment for the action letter is stated below.

Conclusion:

[Redacted] (b) (4)
[Redacted] Office of compliance will need to perform an inspection of the applicant's drug product manufacturing facility (For Cause Inspection) and evaluate the proposed corrective actions. Hence it is recommended that the application be not approved from a CMC perspective.

The draft language for the CR letter is as follows

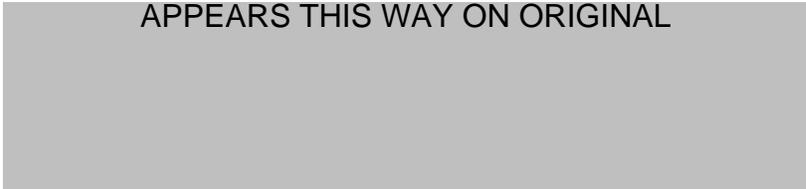
[Redacted] (b) (4)
[Redacted]

[Redacted] (b) (4)
[Redacted] Based on the currently available data provided in the amendment dated Sept 23, 2010, the review division is recommending a "For Cause Inspection" of the drug product manufacturer's facility

[Redacted] (b) (4)
[Redacted] Until an inspection is performed and a satisfactory recommendation issued for all manufacturing sites by the Office of Compliance, the NDA is recommended for a complete response.

Martin Haber, Ph.D.
Chemistry Reviewer, DNDPAIII/ONDQA

APPEARS THIS WAY ON ORIGINAL



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/s/

MARTIN T HABER
09/23/2010

PRASAD PERI
09/24/2010
I concur

NDA 22-396

Dyloject (diclofenac sodium) Injection

**Hospira, Inc
(Formerly Javelin Pharmaceuticals, Inc.)**

**Martin Haber, Ph.D.
Division of Pre-Marketing Assessment I**

**For
Division of Anesthesia, Analgesia, and Rheumatology
Products**

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Chemistry Review Data Sheet

1. NDA 22-396
2. REVIEW #1
3. REVIEW DATE: September 2, 2010
4. REVIEWER: Martin Haber, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

CMC IR

Document Date

6/10/2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original
 Amendment
 Amendment

Document Date

12/2/2009
 12/22/2009 (Carton and vial labels)
 1/14/2010 (DMF number assignment)
 3/18/2010 (Updated stability)
 4/28/2010 (Vial Samples)
 5/25/2010 (Updated stability)
 7/8/2010 (Change in NDA sponsor)
 7/12/2010 (Response to IR)
 7/19/2010 (Response to IR)
 7/28/2010 (Response to IR)
 8/12/2010 (Response to IR)

7. NAME & ADDRESS OF APPLICANT:

Name: Javelin Pharmaceuticals, Inc.,

Address: 125 Cambridge Park Dr, Cambridge, MA 02140

Executive Summary Section

Representative: Roberta Tucker, Acting Vice President

Telephone: 508 842-9339

Note: Javelin Pharmaceuticals was acquired by Hospira, Inc. on 7/8/10, contact addresses remain the same.

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Dyloject
- b) Non-Proprietary Name (USAN): diclofenac sodium
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3 (New Formulation)
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: NSAID Analgesic

11. DOSAGE FORM: Sterile aqueous solution for injection

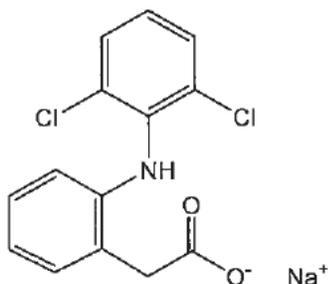
12. STRENGTH/POTENCY: 37.5 mg/mL

13. ROUTE OF ADMINISTRATION: IV (b) (4) Injection14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

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

Executive Summary Section

INN:	Diclofenac sodium
Compendial Name:	Diclofenac sodium, USP
Chemical Name:	Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, monosodium salt
Other Name(s):	Sodium [o-(2,6-dichloroanilino)phenyl]acetate Sodium 2-[(2,6-dichlorophenyl) amino]phenyl]acetate
CAS Registry No:	15307-79-6



MOLECULAR FORMULA: C₁₄H₁₀Cl₂NNaO₂

MOLECULAR WEIGHT: 318.13

Note: USAN name is the same as INN.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	08/11/2010	Reviewed by this reviewer
	II			3	Adequate		Reviewed previously by OGD
	III			4	N/A		Review normally not required.
	III			4	N/A		Review normally not

Executive Summary Section

(b) (4)	III	(b) (4)	1	Adequate	08/16/2010	required. Reviewed by this reviewer
	III		7	Adequate		Reviewed previously by Microbiology

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,048	Diclofenac sodium clinical trials

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	Pending		
Methods Validation	Not required		M. Haber
OSE	Pending		
EA	Categorical Exclusion refused, FONSI pending		
Microbiology	Approval	8/2/10	J. Metcalf

The Chemistry Review for NDA 22-396

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval, pending an acceptable overall manufacturing facilities evaluation and an Environmental Assessment FONSI

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

Not Applicable

II. Summary of Chemistry Assessments

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

The drug product is an aqueous solution presented in a 1 mL fill volume in a 2 mL USP Type I flint glass vial with a 13 mm (b) (4) rubber stopper and aluminum overseal. The active concentration is 3.75%, resulting in a strength of 37.5 mg of diclofenac sodium in 1 mL. (b) (4)

The drug product vial also contains the following excipients: 333 (b) (4) mg hydroxypropyl-beta-dex (β -cyclodextran), 5.0 mg monothioglycerol, and traces of hydrochloric acid/sodium hydroxide added to adjust the pH (b) (4)

A pharmaceutical development report describes manufacturing issues (b) (4)

The drug product is manufactured (b) (4) The facility cGMP status for this site only was acceptable based on the district recommendation as of 3/16/2010. The manufacturing process involves (b) (4)

The release specifications include tests for appearance, identification, color, pH, osmolality, volume in container, hydroxypropyl betadex, monothioglycerol, assay (diclofenac sodium),

Executive Summary Section

related substances (b) (4) individual unknowns, and total unknowns), particulate matter, sterility, bacterial endotoxins and container-closure integrity. The specification limits for osmolality, pH, hydroxypropyl betadex, and the (b) (4) impurity were tightened as requested by the Agency.

The container closure system consists of 2 mL size USP Type I glass vials with 13 mm (b) (4) rubber stoppers and aluminum overseals. The secondary packaging consists of a white cardboard carton holding 25 vials.

Stability studies showed (b) (4). The assay results (b) (4) ranged from (b) (4)%. Test results for all parameters remained within proposed acceptance limits for 18 months at room temperature.

The drug substance, diclofenac sodium, was first approved in the 1970's and is the subject of a USP monograph. There are several previously approved formulations for both the sodium and potassium salt forms. The diclofenac molecule is a weak acid with no chiral centers. The sodium salt is used for this NDA.

The bulk drug substance is manufactured (b) (4). CMC information for the (b) (4) site is provided in DMF (b) (4). DMF (b) (4) was originally submitted in 1991 and has been reviewed multiple times by OGD. The DMF is adequate. (b) (4)

(b) (4) CMC information for the (b) (4) site is provided in DMF (b) (4). DMF (b) (4) was reviewed by this reviewer on 5/25/10 and found inadequate. The DMF was amended with revised drug substance specifications and re-reviewed on 8/11/10 and found adequate. Facility inspections are pending for both sites. The NDA provides little information regarding drug substance manufacturing and cross-references DMF (b) (4) for (b) (4) and DMF (b) (4) for (b) (4).

Drug substance specifications for both sites are provided. Drug substance is tested to be in compliance with the USP monograph. In addition to USP tests, bioburden and bacterial endotoxins tests are added for the (b) (4) site (b) (4) to qualify the use of the drug substance as a component suitable for parenteral use. USP tests include description, identification, assay, chromatographic purity, color of solution, clarity of solution, solution pH, loss on drying, and heavy metals. The NDA sponsor states that likely impurities (b) (4) and residual solvent. They state however that typically no (b) (4) or any other impurity is observed by the validated HPLC method with a limit of detection of (b) (4)%. The specification limits for (b) (4) any

Executive Summary Section

individual unknown related substance were (b) (4) % as requested by the Agency in accordance with the ICH Q3A guideline.

Based on the data collected (b) (4) assigns a (b) (4) retest date to lots of drug substance stored (b) (4). The drug substance is stored (b) (4).

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

Dyloject Injection is a parenteral NSAID indicated for the management of acute pain in adults. The dosage is 37.5 mg (1 mL) administered by intravenous bolus injection. (b) (4) Treatment may be repeated every 6 hours, not to exceed 150 mg/day. The vial is for single use only (b) (4).

The proposed storage condition for the commercial product is controlled room temperature, "Store at Controlled Room Temperature 20-25°C (68-77°F) [see USP]", with a proposed expiration period of (b) (4) months.

C. Basis for Approvability or Not-Approval Recommendation

The firm has adequately responded to all chemistry deficiencies described in the IR letter and other communications. Microbiology sterility assurance review recommends approval. Regarding manufacturing facilities, an EES overall recommendation is pending. Javelin was asked to supply an Environmental Assessment and a Finding Of No Significant Impact (FONSI) is pending.

III. Administrative**A. Reviewer's Signature**

See DARRTS

B. Endorsement Block

See DARRTS

C. CC Block

See DARRTS

74 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

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

/s/

MARTIN T HABER
09/02/2010

PRASAD PERI
09/02/2010
I concur

Initial Quality Assessment
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products

NDA: 22-396
 Applicant: Javelin Pharmaceuticals
 Stamp Date: 12/3/2009
 PDUFA Date: 10/3/10 Standard
 Trademark: Dyloject
 Established Name: diclofenac sodium injection
 Dosage Form and strength: Sterile solution in vial, 37.5 mg/1 mL (b) (4)
 Route of Administration: Injection, IV (b) (4)
 Indication: short term management of pain

PAL: Danae Christodoulou, Ph.D. Branch II/DPA I/ONDQA
 (IQA authored by primary reviewer)

Fileability recommendation: Acceptable for filing

Review team recommendation: Single primary reviewer (Martin Haber, Ph.D)

Time goals:

- **Initial Quality Assessment in DFS:** by 1/21/10
- **Chemistry filing memo in DFS:** by 1/21/10
- Filing decision “Day 45”: 1/21/10 (tentative; to be set by Clinical Division)
- Filing review issues “Day 74”: 2/15/10 (tentative; to be set by Clinical Division)
- **Chemistry Review (DR/IR) letter:** by 5/3/2010
- Mid-cycle meeting “Month 5”: 5/3/2010
- Wrap Up: 8/3/2010
- **Final Chemistry Review “Month 8” in DFS:** by 8/3/2010
- PDUFA: 6/3/2010 if Priority Review, 10/3/10 if Standard

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	To be determined by Primary Reviewer
EA	To be assessed by Primary Reviewer
EES	EER sent to Office of Compliance on 12/14/2009
DMETS	<i>Labeling consult request will be sent by clinical division</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	<i>Consult sent, reviewer pending</i>
Pharm/Tox	<i>DS and DP Impurities to be qualified</i>

Summary:

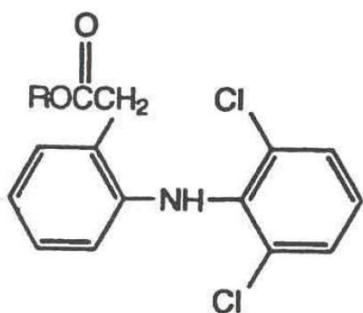
Electronic NDA in CTD format with Quality Overall Summary. The NDA was filed as a 505(b)(2) application with Cataflam (diclofenac potassium) from Novartis as the RLD.

Drug Substance

Diclofenac originated around 1973 and is a compendial NSAID available as a generic drug in several oral formulations. Both sodium and potassium salt forms are available.

INN:	Diclofenac sodium
Compendial Name:	Diclofenac sodium, USP
Chemical Name:	Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, monosodium salt
Other Name(s):	Sodium [o-(2,6-dichloroanilino)phenyl]acetate Sodium 2-[(2,6-dichlorophenyl) amino]phenyl]acetate
CAS Registry No:	15307-79-6

Note: USAN name is the same as INN.



R= Na

Molecular Formula:	C ₁₄ H ₁₀ Cl ₂ NNaO ₂
Molecular Weight:	318.13
Stereochemistry:	Not applicable

Physical appearance: White, crystalline, odorless powder; slightly hygroscopic
Solubility: Water (b) (4)
Methanol (b) (4)
Ether (b) (4) practically insoluble
Odor: Odorless
Melting point: (b) (4)
UV spectrum: (b) (4)
Dissociation constant (pKa): (b) (4)
Partition coefficient: (b) (4)
Hygroscopicity: Slight
Polymorphism: (b) (4)

The bulk drug substance is manufactured (b) (4)
The (b) (4) site performs the (b) (4)

Manufacturing information is provided in Type II DMF (b) (4) ((b) (4) site) and DMF (b) (4) site), holder is (b) (4) for both. DMF (b) (4) was originally submitted in 1991 and it has been reviewed 4 times by OGD, most recently on 8/6/2007 by Yusuf Amin, and found adequate. (b) (4)

The (b) (4) DMF (b) (4) was also found adequate. The drug substance is (b) (4) DMF (b) (4) is new and will require review. Manufacturing at the (b) (4) site consists of (b) (4) the drug substance. Complete copies of both DMFs have been received.

Batch release data is provided in the NDA for three (b) (4) kg scale batches manufactured at the (b) (4) site in 2007. Batch release data is provided for three (b) (4) kg scale batches manufactured at the (b) (4) site in June 2009 along with data from three more recent batches from the (b) (4) site for comparison. Assay values were (b) (4)% and impurity levels were (b) (4). Loss on drying results ranged from (b) (4)%. Residual solvent results ranged from (b) (4) ppm.

Specifications are based on the USP monograph, see attached table:

Table 3.2.S.4.1-1: Proposed Tests and Specifications for Diclofenac Sodium

Test		Specification
Description		White to off-white, crystalline powder
Identification A USP ^{a,b}		Infrared Absorption (Pass)
Identification B USP ^b		The retention time of the diclofenac peak in the chromatogram of the Test solution corresponds to that of the Resolution solution as obtained in the test for Chromatographic purity. (Pass)
Identification C USP ^{a,b} (sodium)		The residue obtained by igniting it responds to the flame test for Sodium (Pass)
Color of Solution USP ^{a,b}		A 1 in 20 solution of diclofenac sodium in methanol is colorless to faintly yellow, and the absorbance of the solution, determined in a 1-cm cell at 440 nm, is not more than 0.050, methanol being used as the blank. (Pass)
Clarity of Solution USP ^{a,b}		The solution prepared as directed under Color of solution is not significantly less clear than an equal volume of methanol contained in a similar vessel and examined similarly. (Pass)
Loss on Drying ^{a,b,c}	USP <731>	It loses NMT 0.5% of its weight
Residual Solvents	USP <467>	NMT (b) (4)% (NMT (b) (4) ppm)
Bioburden ^{a,b}	USP <61>	NMT (b) (4) CFU/g total aerobic NMT (b) (4) CFU/g total yeasts and molds
Bacterial Endotoxins ^{a,b}	USP <85>	NMT (b) (4) EU/mg

Test		Specification
pH solution (1 in 100) USP ^{a,b}		7.0 - 8.5
Heavy Metals USP ^b		≤ (b) (4)%
Chromatographic Purity USP ^{a,b}		(b) (4); ^d ≤ (b) (4)% Any other individual impurity: ≤ (b) (4)% Total amount of impurities: ≤ (b) (4)%
Assay ^{a,b} USP		99.0% - 101.0%

NMT: not more than

^a Tests performed by the drug substance manufacturer

^b Tests performed by the drug product manufacturer upon receipt of drug substance from the drug substance manufacturer

^c Test includes control of (b) (4)

^d Also known as (b) (4)

(b) (4)
Bioburden and endotoxin testing are added to USP specifications.

Quantitative sodium test should be added. Particle size is mentioned in DMF review but is not part of final specifications. Residual solvent refers to (b) (4) according to ICH Q3C guidance.

The justifications for all specifications and impurities limits will need evaluation during review since this NDA is for an injectable drug product and requires higher quality material. The major impurity, (b) (4) see structures and discussion below. Specification justifications can be reviewed as part of the review of the second DMF, DMF (b) (4)

Drug substance stability appears adequate, according to the previous DMF review. The drug substance is stored (b) (4). This discrepancy will need to be resolved during the review. Also, it should be determined if stress testing is adequate. Possibly the drug substance (b) (4) in this formulation.

Drug Product

The drug product is an aqueous solution presented in 1 mL (b) (4) fill volumes in 2 mL USP Type I flint glass vials with 13 mm (b) (4) rubber stoppers and aluminum overseals. The active concentration is constant (3.75%), resulting in (b) (4) 37.5 mg/1 mL (b) (4). The normal dosage regimen is 37.5 mg every six hours (b) (4).

There are two major compendial excipients, (b) (4) see table below. (b) (4) monothioglycerol, is found in the Inactive Ingredients Guide under "thioglycerol" and has been used in injection products up to 1.0%. (b) (4)

(b) (4) Betadex is found in the Inactive Ingredients Guide but no listing was found for Hydroxypropyl betadex. Hydroxypropyl betadex is the USP name for hydroxypropyl β -cyclodextran, a cyclic compound containing seven α -(1,4) linked glucopyranosyl units partially substituted with poly(hydroxypropyl) ethers. (b) (4)

The NDA cover letter references Sporanox, NDA 20-966, to support the use

of the hydroxypropyl betadex excipient (b) (4) This NDA is listed as withdrawn pending FR notice in DARRTS.

(b) (4)

Table 3.2.P.1-1: Unit-Dose Composition of the Drug Product

Ingredient	Amount (mg/1 mL)	(b) (4)	Concentration (% w/v)	Function	Reference
Diclofenac Sodium	37.5		3.75	Drug substance	USP
Hydroxypropyl-Betadex	333 (b) (4)		(b) (4)	(b) (4)	NF
Monothioglycerol	5.0		0.5		NF
Hydrochloric Acid/Sodium Hydroxide				pH adjustment (b) (4)	NF
Water for Injection					USP (b) (4)

A pharmaceutical development report is provided, as requested by the Agency. Formulation development focused on providing a formulation that could be administered as an IV bolus (b) (4)

Other development issues: The osmolality should be (b) (4) and the container/closure system should be suitable for an injectable. The shelf life should be satisfactory (b) (4)

(b) (4)

(b) (4). Vials are for single use only (b) (4).

(b) (4)
Adequacy of these factors will be evaluated during the NDA review.

Key manufacturing process steps are (b) (4)

A flow chart and a detailed complete description of the manufacturing process is provided. Note:

The product (b) (4) microbial controls and sterility assurance are critical for this product. A sterility validation report is provided in CTD 3.2.P.3.5.

(b) (4)

Photostability studies of the drug product suggest that the drug substance is photosensitive.

(b) (4)

Clear glass was chosen instead and the carton container is used to protect the vials from light. The selected stopper (b) (4)

A leachables study on the selected stopper and vial with the drug product solution (betadex containing) showed no appreciable level of and no accumulation of extractable or leachable materials (b) (4). The provided report is very brief and not clear. Additional information will be requested during review. Additional safety information is provided in the container/closure DMFs.

The drug product is manufactured (b) (4). Full-size, production scale commercial batches are (b) (4) L, corresponding to about (b) (4) vials of the 37.5 mg/1 mL presentation and using about (b) (4) kg of drug substance.

Table 3.2.P.5.1-1: Proposed Specifications for Commercial Batches of Dyloject

Test	Acceptance Criteria	Method References
Appearance	Clear, colorless liquid in a 2 mL vial with the appropriate flip-off cap: 1 mL presentation – orange cap (b) (4)	Visual
Identification (HPLC)	RT of the sample peak corresponds to that of the standard	TM D136 CTD 3.2.P.5.2
Identification (IR)	Sample IR spectrum corresponds to that of the reference spectrum	USP <197F>
Color	NMT (b) (4)	USP <851>
pH	(b) (4)	USP <791>
Osmolality	(b) (4) mOsm/kg	USP <785>
Volume in Container ^a	NLT 1.0 mL/vial (1 mL presentation) (b) (4)	USP <1>
Hydroxypropyl Betadex	(b) (4) (b) (4) mg/2 mL (2 mL presentation) (b) (4)	TM D137 CTD 3.2.P.5.2
Monothioglycerol	Release: (b) (4) Stability: (b) (4)	TM D138 CTD 3.2.P.5.2
Assay (Diclofenac Sodium)	Release: (b) (4) Stability: (b) (4)	TM D136 CTD 3.2.P.5.2

Test	Acceptance Criteria	Method References
Related Substances	(b) (4) NMT (b) (4) % w/w ^b	TM D136 CTD 3.2.P.5.2
	Individual Unknown NMT (b) (4) % area	
	Total Unknown NMT (b) (4) % area	
Particulate Matter	Release: Particles ≥ (b) (4) NMT (b) (4) Particles ≥ (b) (4) NMT (b) (4) Stability: Particles ≥ (b) (4) NMT (b) (4) Particles ≥ (b) (4) NMT (b) (4)	USP <788>
Sterility	Sterile	USP <71>
Bacterial Endotoxins	NMT (b) (4) EU/mL (IU/mL)	USP <85>
Container-Closure Integrity ^c	No leakage	Visual Inspection CTD 3.2.P.5.2

^a Performed only on labeled or inspection samples

^b This level is qualified per ICH Q3B(R2); see CTD Module 4.2.3.7.6

^c Performed (b) (4)

Batch release results are provided for drug product manufactured by (b) (4) and two other firms, (b) (4) who manufactured some preclinical and clinical batches, using (b) (4) drug substance manufactured at the (b) (4) site. Batch release results are also provided for one batch using (b) (4) drug substance made at the (b) (4) site. All proposed specifications for batch release are met.

(b) (4)

A separate specification limit at release (b) (4) should be established.

Chemical structures of possible diclofenac impurities are shown in the following table.

Table 3.2.S.3.2-1: Chemical Structures of Diclofenac Impurities

Impurity	Structure
(b) (4)	

(b) (4)

Justifications for proposed specifications are provided. The osmolality test specification is (b) (4) based on batch release results (b) (4) and stability results (b) (4). Assay specification limit is (b) (4) based on release results (b) (4) and the stability limit is (b) (4) % based on stability results (b) (4).

The proposed related substances limits were set (b) (4) The limit (b) (4) has been (b) (4) NMT (b) (4) % (b) (4) The limit for total unknown related substances is NMT (b) (4) % (b) (4) The total was (b) (4) at release. In accordance with ICH guidance, individual unknowns are limited to NMT (b) (4) %.

The hydroxypropyl betadex release specification is (b) (4) % based on a range of (b) (4) % observed in batch release data. The monothioglycerol release specification is (b) (4) % based on batch release range of (b) (4) % observed to date. Both could be tightened. The stability limit for monothioglycerol is (b) (4) % (b) (4) The (b) (4) manufacturing process is (b) (4)

Other test limits follow USP, i.e., sterility and bacterial endotoxins. The pH limit is (b) (4) This should be evaluated during NDA review.

Volume in container limit is NLT 1.0 mL (b) (4) Particulate matter specifications were tightened as requested by the Agency to NMT (b) (4) particles \geq (b) (4) μm and NMT (b) (4) particles \geq (b) (4) μm at release and to (b) (4) that number of particles on stability.

Reference standards are based on USP materials except that the monothioglycerol standard is not available. A suitable commercial sample was purchased.

The primary packaging used for both strengths consists of a USP Type I glass vial, size 2 mL, and 13 mm (b) (4) rubber stoppers (b) (4) and aluminum overseals. There are two suppliers for the vial, (b) (4) The cap for the 1 mL presentation is orange (b) (4) The secondary packaging consists of a white cardboard carton which holds 25 vials and provides protection from light.

Seven primary stability batches were manufactured (b) (4) and stored (b) (4) at 25°C/60%RH and 30°C/monitored RH in cartons (b) (4) (same carton material as commercial package). Twelve months of data are available. Three supportive stability batches manufactured (b) (4) have 24 months of data available. All stability results comply with the proposed specifications.

(b) (4)

(b) (4) Whatever this really means will be evaluated during NDA review.

A photostability study on the clinical batch showed that the drug product is susceptible to photodegradation and should be protected from light.

The proposed storage condition for the commercial product is controlled room temperature with a proposed expiration period of (b) (4) months. This will be evaluated during NDA review. (b) (4)

(b) (4) Executed batch record is provided. A method validation package is provided.

CRITICAL ISSUES

- Has all information requested during the IND phases, and at the pre-NDA meetings been included? Yes. Excipient review by Clinical Pharmacology and/or pharmacology/toxicology may be required.
- GMP status of the drug substance/drug product manufacturing sites. All sites (3) have been submitted for EES evaluation.
- The justifications for all specifications and impurities limits for drug substance and drug product will need evaluation during review since this NDA is for an injectable drug product and requires higher quality material.

Supporting NDA or IND: IND 65,048

Supporting DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	LOA is provided. Review of Annual reports needed.
	II			LOA is provided. Review needed
	III			Review normally not required.
	III			Review normally not required.
	III			Reviewed previously.

DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
(b) (4)	III		(b) (4)	Reviewed previously by Microbiology.

CHEMISTRY NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		12 months stability data provided.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		

Preliminary CMC comments for the 74 day letter

None.

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

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

/s/

MARTIN T HABER
02/23/2010

PRASAD PERI
02/26/2010
I concur