

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-239

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: July 13, 2009

FROM: David J. Claffey, Ph.D., ONDQA

SUBJECT: **Updated Office of Compliance recommendation for
NDA 22-239**

The Office of Compliance issued a 'withhold' recommendation for NDA 22-239 on 1 JUL 2009 for this application. This recommendation was updated to 'acceptable' on 13 JUL 2009 (refer to Attachment). An approval recommendation from a CMC perspective can now be made.

ATTACHMENT

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Application:	NDA 22239/000	Action Goal:	
Stamp Date:	31-DEC-2007	District Goal:	16-MAY-2009
Regulatory:	15-JUL-2009		
Applicant:	ZOGENIX INC 1400 SOUTH ORANGE AVE ORLANDO, FL 32806	Brand Name:	SUMATRIPTAN
		Estab. Name:	
		Generic Name:	SUMATRIPTAN
Priority:	3S	Dosage Form:	(INJECTION)
Org. Code:	120	Strength:	6 MG/0.5 ML

Application Comment: THIS APPLICATION IS FOR A DRUG/DEVICE COMBINATION. THE PRODUCT IS A DISPOSABLE, PRE-FILLED, NEEDLE-FREE, INJECTOR FOR SUBCUTANEOUS DELIVERY OF SUMATRIPTAN. THE DELIVERY DEVICE IS NOVEL. (on 01-FEB-2008 by M. HEIMANN () 301-796-1678)

FDA Contacts:	S. GOLDIE	Project Manager	301-796-2055
	D. CLAFFEY	Review Chemist	301-796-1343
	M. HEIMANN	Team Leader	301-796-1678

Overall Recommendation:	ACCEPTABLE	on 13-JUL-2009	by E. JOHNSON	(HFD-320)	301-796-3334
	WITHHOLD	on 01-JUL-2009	by E. JOHNSON	(HFD-320)	301-796-3334
	ACCEPTABLE	on 07-MAR-2008	by S. ADAMS	()	301-827-2443

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

DMF No: (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Estab. Comment:

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	08-FEB-2008				GOLDIES
OC RECOMMENDATION	11-FEB-2008			ACCEPTABLE	ADAMSS
				BASED ON PROFILE	

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

Establishment: CFN: 9610802 FEI: 3002807216
 PATHEON UK LIMITED
 KINGFISHER DRIVE
 COVINGHAM, SWINDON, WILTSHIRE, UNITED KINGDOM

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Estab. Comment: A KTM MAY BE ISSUED FOR THIS ESTABLISHMENT THAT IS NAMED IN THIS APPLICATION. PLEASE CONTACT TARA GOOEN OR COKI CRUZ FOR MORE INFORMATION. (on 04-MAY-2009 by M. STOCK (HFD-320) 301-796-4753)
 PATHEON UK PERFORMS (b) (4) OF THE DRUG FORMULATION, RELEASE TESTING, AND STABILITY TESTING, PATHEON ALSO PERFORMS ASSEMBLY OF SOME DEVICE SUB-COMPONENTS, FINAL ASSEMBLY OF THE DEVICE, AND LABELING/PACKAGING. (on 01-FEB-2008 by M. HEIMANN () 301-796-1678)
 THE MAIN BACKGROUND: IN THE CLINICAL STUDY, THERE WERE SOME ISSUES WITH DRUG NOT PENETRATING THE SKIN ON THE ARM AND HIGH VARIABILITY. THIS DEVICE WORKS BY THE JET OF SOLUTION PUNCHING A HOLE IN THE SKIN TO ALLOW DRUG TO ENTER. THE CMC SPECIFICATIONS DO NOT TEST THE FORCE OF THE JET (ONLY THE AMOUNT OF SOLUTION EMITTED). THE JET FORCE IS CONTROLLED BY HOW THE DEVICE IS MANUFACTURED (MAINLY THE FORCE FROM THE COMPRESSED GAS AND THE SIZE OF THE ORIFICE THE SOLUTION MUST PASS THROUGH). THIS IS WHY I THOUGH THE INSPECTION WOULD BE IMPORTANT FOR THE QUALITY OF THIS PRODUCT.

(on 31-MAR-2009 by S. FERGUSON (HFD-322) 301-796-3247)
 US AGENT FRANCIS P MCCUNE
 DIRECTOR OF LEGAL SERVICES
 PATHEON PHARMACEUTICALS, INC
 2110 EAST GALBRAITH ROAD
 CINCINNATI, OH 45237
 (513) 948-7699
 FRANK.MCCUNE@PATHEON.COM (on 08-FEB-2008 by S. GOLDIE () 301-796-2055)

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	08-FEB-2008				GOLDIES
SUBMITTED TO DO	11-FEB-2008	10-Day Letter			ADAMSS
DO RECOMMENDATION	07-MAR-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	07-MAR-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	31-MAR-2009				FERGUSONS
SUBMITTED TO DO	31-MAR-2009	GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	31-MAR-2009	Product Specific			JOHNSONE
INSPECTION SCHEDULED	07-MAY-2009		24-JUN-2009		IRIVERA
DO RECOMMENDATION	01-JUL-2009			WITHHOLD INADEQUATE ENVIRONMENT CONTROL	JOHNSONE
				FIRM HAS NOT DEMONSTRATED CEPHALOSPORIN CONTAINMENT - WITHHOLD PENDING ACCEPTABLE RESPONSE	
OC RECOMMENDATION	01-JUL-2009			WITHHOLD DISTRICT RECOMMENDATION	JOHNSONE
DO RECOMMENDATION	13-JUL-2009			ACCEPTABLE ADEQUATE FIRM RESPONSE	JOHNSONE
				BASED ON R. ARROYO REVIEW AND C. ROSA CONCURRENCE.	
OC RECOMMENDATION	13-JUL-2009			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE

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/s/

David Claffey
7/13/2009 02:35:04 PM
CHEMIST

Ramesh Sood
7/13/2009 02:37:11 PM
CHEMIST

NDA 22-239

SumavelTM DoseProTM
(Sumatriptan injection)

Zogenix, Inc.

Review #2

David J. Claffey, PhD
ONDQA

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Chemistry Review Data Sheet

1. NDA 22-239
2. REVIEW #: 2
3. REVIEW DATE: 8 JUL 2009.
4. REVIEWER: David J. Claffey, PhD

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Application	28 DEC 2007
Amendment N-001	6 FEB 2008
Amendment N-003	2 MAY 2008
Amendment N-004	19 MAY 2008
Amendment N-007	28 JUL 2008
Amendment N-010	14 AUG 2008
Amendment N-011	18 AUG 2008
Amendment N-012	28 AUG 2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
N-020	14 JAN 2009
N-025	20 MAY 2009

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Zogenix, Inc.
Address: 5858 Horton St, Emeryville, CA 94609.
Representative: Edward F. Smith III, PhD
Telephone: 510 550 8325

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: SUMAVEL™ DosePro™
- b) Non-Proprietary Name (USAN): Sumatriptan succinate
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 5
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: selective 5-hydroxytryptamine receptor subtype 1 agonist for the acute treatment of migraine attacks with or without aura and for the acute treatment of cluster headache episodes.

11. DOSAGE FORM: Injection (subcutaneous needle-free)

12. STRENGTH/POTENCY: 6 mg

13. ROUTE OF ADMINISTRATION: subcutaneous

14. Rx/OTC DISPENSED: Rx OTC

Chemistry Review Data Sheet

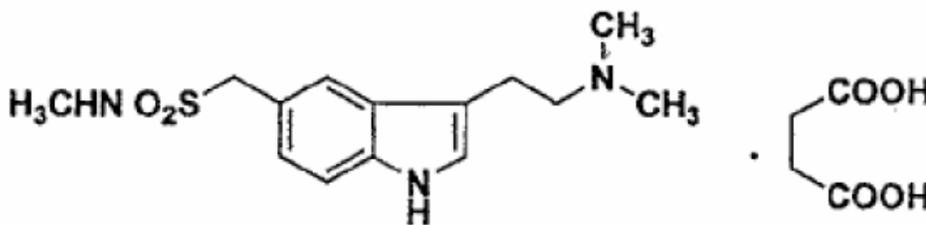
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

 x Not a SPOTS product

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

[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]-Nmethylmethanesulphonamide hydrogen butanedioate



Molecular formula: C₁₈H₂₇N₃O₆S

Molecular weight: 413.40

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4			
	III		4				
	I		4				
	II		3		<i>Adequate</i>	4 SEP 2008 (David J. Claffey, PhD)	
	I		4				

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	(b) (4)	4			
	III			4			
	III			4			

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	71,275	Sumatriptan Intraject

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Withhold*	1 JUL 2009	S Adams
Pharm/Tox	Approval		D. Charles Thompson
CDRH	Concurred with this reviewer's evaluation	4 SEP 2008	William M. Burdick
Microbiology	Approval	27 AUG	John Metcalfe, PhD



CHEMISTRY REVIEW



Chemistry Review Data Sheet

		2008	
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* note that the overall acceptable recommendation of 7 MAR 2008 was changed to a Withhold recommendation on 1 JUL 2009.

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.

Yes No If no, explain reason(s) below:

The Chemistry Review for NDA 22-239

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Compliance issued a 'WITHHOLD' recommendation on 1 JUL 2009 for this application. An approval recommendation from a CMC perspective is contingent on the resolution of the compliance issues and the issue of an 'acceptable' recommendation from the Office of Compliance.

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

N/A

II. Summary of Chemistry Assessments

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

The proposed drug product, SUMAVEL™ DosePro™ (sumatriptan injection) is a drug-device combination product. It is a sterile, pre-filled, disposable, needle-free delivery system, designed to deliver 6 mg/0.5 mL aqueous dose of sumatriptan (as the succinate salt) into the patient's subcutaneous tissue. It is the same dose and concentration as the existing marketed injectable formulation (IMITREX® Injection 6 mg). The drug substance sumatriptan succinate is a white water-soluble compound whose CMC details were cross referenced to DMF (b) (4). This DMF was initially found to be deficient by this reviewer, however all outstanding issues were resolved in this review cycle. The drug substance controls at the drug product manufacturing site were found to be generally adequate, consisting of a basic ID, appearance and check of the CoA (after vendor qualification using a more extensive list of tests). Drug substance specifications generally complied with those described in the recent USP monograph for sumatriptan succinate. The administered drug product solution is simply composed of 0.5 ml of 12 mg/ml drug substance in an isotonic saline solution. The solution is (b) (4)

The drug product is manufactured by Patheon UK Ltd. The manufacturing process involves several distinct operations - (b) (4)

Executive Summary Section

(b) (4) The drug product solution does not contain a preservative. Its sterility is assured by the (b) (4) operations and the (b) (4). The drug product container closure (capsule sub-assembly) is designed to protect the integrity of the drug formulation solution by preventing microbial contamination. The components are designed with interfering (i.e. overlapping) tolerances such that the assembly is sealed to prevent formulation egress and microbial and other foreign contamination ingress. Further assurance of acceptable microbial quality is provided by the testing of each drug product lot at release for sterility and bacterial endotoxins. Studies demonstrated that the drug product contact components did not significantly impact product quality through adsorption, leachables or extractables. No changes were made to the formulation during development nor were any changes made to the device that would significantly affect its performance across the pivotal clinical studies. Real time stability data supported the proposed 24-month drug product expiry period.

It should be noted that the Office of Compliance issued an “acceptable” recommendation for this application on 7 MAR 2008. On April 2009 the OC took an internal decision to schedule an inspection of the drug product manufacturing site as part of a pilot program. It was as a result of this June 2009 inspection that a 483 was issued resulting in the OC’s “withhold” recommendation.

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

The proposed indications are for the acute treatment of migraine attacks with or without aura and for the acute treatment of cluster headache episodes. The drug product is to be administered subcutaneously into the abdomen or thigh (not the arm) as a single dose not to exceed 6 mg. No more than two 6 mg doses – separated by one hour - should be administered within 24 hours.

C. Basis for Approvability or Not-Approval Recommendation

An approval action is recommended based on:

- the data submitted in this Application and on the various responses to the information requests.
- The microbiological reviewer’s approval recommendation (27 AUG 2008).
- CDRH concurrence with this reviewers recommendation (Attachment 2 of this review).
- The resolution of the deficiencies associated with the cross referenced DMF (b) (4)
- Resolution of the issue concerning the acceptance criteria for drug product impurities 1 and 2.

Executive Summary Section

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

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page as B4 (TS/CCI)**

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/s/

David Claffey
7/10/2009 12:13:33 PM
CHEMIST

Ramesh Sood
7/10/2009 03:10:34 PM
CHEMIST

CMC BRANCH CHIEF MEMORANDUM

To: NDA 22-239
From: Ramesh Sood, Ph.D., Branch Chief, ONDQA
Date: 14-Oct-2008
Drug: Sumavel™ DosePro™ (sumatriptan) Injection
Route of administration: Subcutaneous Injection
Strength: 6 mg/0.5 ml.
Subject: **Approval** recommendation for NDA 22-239

Introduction: Sumatriptan succinate and sumatriptan are marketed by the innovator firm, GlaxoSmithKline, as Imitrex® under three approved applications, NDA 20-080 (Imitrex Injection, 4 mg/0.5 mL and 6 mg/0.5 mL), NDA 20-132 (Imitrex Tablets, 25 mg, 50 mg and 100 mg) and NDA 20-626 (Imitrex Nasal Spray, 5 mg and 20 mg). Zogenix, Inc., has submitted a 505 (b)(2) application to market the proposed drug product, SUMAVEL™ DosePro™ (sumatriptan) injection is a drug-device combination product. It is a sterile, pre-filled, disposable, needle-free delivery system, designed to deliver 6 mg/0.5 ml aqueous dose of sumatriptan (as the succinate salt) into the patient's subcutaneous tissue. It is the same dose and concentration as the existing marketed injectable formulation (IMITREX® Injection 6 mg).

Drug Substance: The active ingredient, sumatriptan succinate [[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]-N-methylmethanesulphonamide butanedioate (1:1)], is a well characterized small molecule with molecular formula C₁₈H₂₇N₃O₆S and molecular weight 413.40. The drug substance is freely soluble in water. The bulk drug substance will be supplied by (b) (4) and the CMC information for the bulk drug substance is incorporated by cross-reference to DMF (b) (4). The CMC reviewer initially found this DMF to be inadequate. However, the DMF holder has responded to the deficiencies and the DMF is now adequate to support the current NDA. The drug substance controls at the drug product manufacturing site were found to be generally adequate, consisting of a basic ID, appearance and check of the CoA (after vendor qualification using a more extensive list of tests). The drug substance specification proposed by the DMF holder generally complied with those described in the recent USP monograph for sumatriptan succinate.

Drug product: The Sumavel™ DosePro™ system is a pre-filled, disposable, single use, needle-free injector device designed for subcutaneous delivery of 0.5 mL of a sterile aqueous solution containing sumatriptan succinate (b) (4), equivalent to 6 mg sumatriptan base). The DosePro™ system is designed for patient self-administration with ease of administration and safe disposal without risk of needle injury being the potential advantages over the current injection systems. All device manufacturing steps except assembly of the actuator sub-assemblies are performed by the drug product manufacturer, Patheon UK, Ltd; actuators are assembled by Bespak.

The drug product formulation is a simple solution composed of 0.5 ml of 12 mg/ml drug substance in an isotonic saline solution. The solution is (b) (4).

The drug product is manufactured by Patheon UK Ltd. The manufacturing process involves several distinct operations - (b) (4)

The drug product solution does not contain any preservative. Its sterility is assured by the (b) (4) operations and the (b) (4)

The drug product container closure (capsule sub-assembly) is designed to protect the integrity of the drug formulation solution by preventing microbial contamination. The components are designed with interfering (i.e. overlapping) tolerances such that the assembly is sealed to prevent formulation egress and microbial and other foreign contamination ingress. Further drug product quality is assured through appropriate in-process controls and final drug product specification. The drug product specification include tests and acceptance limits for appearance, bacterial endotoxins, sterility, identification (HPLC and UV), assay (HPLC), pH, impurities (HPLC), dose accuracy (gravimetric) and bubble size (visual). The studies have also demonstrated that the drug product contact components did not significantly impact product quality through adsorption, leachables or extractables.

The provided real time stability data support the proposed 24-month drug product expiry period. The proposed drug product impurity limits of NMT (b) (4) and NMT (b) (4) for impurity 1 and 3, respectively, have been accepted by the CMC reviewer based on the submitted batch release and stability data. The applicant has also claimed that the non-clinical studies to support the qualification of these impurities at these levels have been submitted to the agency. The final acceptance of these non-clinical study results by the pharm/tox reviewer was not determined at the time of writing this memorandum. Therefore, 24-month product expiration date by the CMC reviewer is based on the acceptance of the qualification of these two impurities by the pharm/tox reviewer. Should lower limits for these impurities be found to be necessary, a reevaluation of the drug product expiry period and product shelf-life specification will be required.

The microbiology and CDRH reviewers have determined that the provided information to control microbiological quality and the device information, respectively, is adequate.

The Office of Compliance has provided an overall acceptable recommendation for the manufacturing sites.

Recommendation: All CMC related issues had been resolved for this application. The application is recommended for “**Approval**” from the CMC perspective in its current form.

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/s/

Ramesh Sood
10/15/2008 08:13:59 AM
CHEMIST

NDA 22-239

**Sumavel™ DosePro™
(Sumatriptan injection)**

Zogenix, Inc.

**David J. Claffey, PhD
ONDQA**

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Chemistry Review Data Sheet

1. NDA 22-239
2. REVIEW #: 1
3. REVIEW DATE: 25 September 2008.
4. REVIEWER: David J. Claffey, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original Application	28 DEC 2007
Amendment N-001	6 FEB 2008
Amendment N-003	2 MAY 2008
Amendment N-004	19 MAY 2008
Amendment N-007	28 JUL 2008
Amendment N-010	14 AUG 2008
Amendment N-011	18 AUG 2008
Amendment N-012	28 AUG 2008

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: Zogenix, Inc.
Address: 5858 Horton St, Emeryville, CA 94609.
Representative: Edward F. Smith III, PhD
Telephone: 510 550 8325

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: SUMAVEL™ DosePro™
b) Non-Proprietary Name (USAN): Sumatriptan succinate
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 5
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: selective 5-hydroxytryptamine receptor subtype 1 agonist for the acute treatment of migraine attacks with or without aura and for the acute treatment of cluster headache episodes.

11. DOSAGE FORM: Injection (subcutaneous needle-free)

12. STRENGTH/POTENCY: 6 mg

13. ROUTE OF ADMINISTRATION: subcutaneous

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

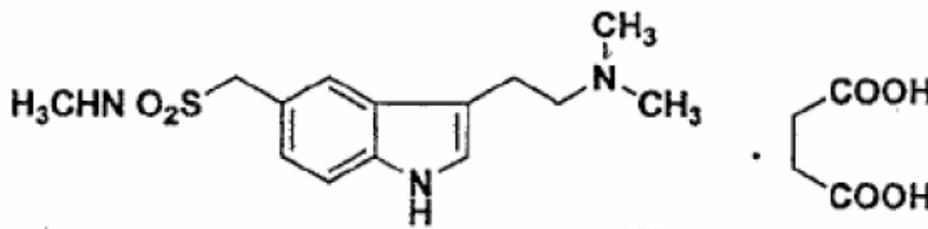
SPOTS product – Form Completed

Chemistry Review Data Sheet

 x Not a SPOTS product

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

[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]-Nmethylnmethanesulphonamide hydrogen butanedioate



Molecular formula: C₁₈H₂₇N₃O₆S

Molecular weight: 413.40

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4			
	III		4				
	I		4				
	II		3		<i>Adequate</i>	4 SEP 2008 (David J. Claffey, PhD)	
	I		4				
	III		4				
	III		4				
	III		4				

Chemistry Review Data Sheet

		(b) (4)					
(b) (4)	III		(b) (4)	4			

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	71,275	Sumatriptan Intraject

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Overall Acceptable	7 MAR 2008	S Adams
Pharm/Tox	Pending		
Biopharm	Pending		
CDRH	Concurred with this reviewer's evaluation	4 SEP 2008	William M. Burdick
Microbiology	Approval	27 AUG 2008	John Metcalfe, PhD

Chemistry Review Data Sheet

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.
 Yes No If no, explain reason(s) below:

The Chemistry Review for NDA 22-239

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

An approval action from a CMC perspective is recommended subject to the acceptance of the pharm/tox reviewer of the proposed acceptance criteria for drug product impurities 1 and 3. Should lower limits for these impurities be found to be necessary a reevaluation of the drug product expiry period will be required. All other outstanding CMC issues have been resolved.

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

N/A

II. Summary of Chemistry Assessments

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

The proposed drug product, SUMAVEL™ DosePro™ (sumatriptan injection) is a drug-device combination product. It is a sterile, pre-filled, disposable, needle-free delivery system, designed to deliver 6 mg/0.5 mL aqueous dose of sumatriptan (as the succinate salt) into the patient's subcutaneous tissue. It is the same dose and concentration as the existing marketed injectable formulation (IMITREX® Injection 6 mg). The drug substance sumatriptan succinate is a white water-soluble compound whose CMC details were cross referenced to DMF (b) (4). This DMF was initially found to be deficient by this reviewer, however all outstanding issues were resolved in this review cycle. The drug substance controls at the drug product manufacturing site were found to be generally adequate, consisting of a basic ID, appearance and check of the CoA (after vendor qualification using a more extensive list of tests). Drug substance specifications generally complied with those described in the recent USP monograph for sumatriptan succinate. The administered drug product solution is simply composed of 0.5 ml of 12 mg/ml drug substance in an isotonic saline solution. The solution is (b) (4)

. The drug product is manufactured by Patheon UK Ltd. The manufacturing process involves several distinct operations - (b) (4)

Executive Summary Section

(b) (4)

The drug product solution does not contain a preservative. Its sterility is assured by the (b) (4) operations and the (b) (4)

The drug product container closure (capsule sub-assembly) is designed to protect the integrity of the drug formulation solution by preventing microbial contamination. The components are designed with interfering (i.e. overlapping) tolerances such that the assembly is sealed to prevent formulation egress and microbial and other foreign contamination ingress. Further assurance of acceptable microbial quality is provided by the testing of each drug product lot at release for sterility and bacterial endotoxins. Studies demonstrated that the drug product contact components did not significantly impact product quality through adsorption, leachables or extractables. No changes were made to the formulation during development nor were any changes made to the device that would significantly affect its performance across the pivotal clinical studies. Real time stability data supported the proposed 24-month drug product expiry period.

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

The proposed indications are for the acute treatment of migraine attacks with or without aura and for the acute treatment of cluster headache episodes. The drug product is to be administered subcutaneously into the abdomen or thigh (not the arm) as a single dose not to exceed 6 mg. No more than two 6 mg doses – separated by one hour - should be administered within 24 hours.

C. Basis for Approvability or Not-Approval Recommendation

An approval action is recommended based on:

- the data submitted in this Application and on the various responses to the information requests.
- The microbiological reviewer's approval recommendation (27 AUG 2008).
- CDRH concurrence with this reviewer's recommendation (Attachment 2 of this review).
- The resolution of the deficiencies associated with the cross referenced DMF (b) (4)
- The overall acceptable recommendation from the Office of Compliance (Attachment 1 of this review).

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

Executive Summary Section

B. Endorsement Block

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

**88 pages withheld
immediately after this page
as B4 (TS/CCI)**

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

/s/

David Claffey
10/10/2008 04:58:21 PM
CHEMIST

Ramesh Sood
10/14/2008 08:20:14 AM
CHEMIST

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division: Division of Neurology Products
NDA: 22-239
Applicant: Zogenix, Inc.
Stamp Date: 31-Dec-2007
PDUFA Date: 31-Oct-2008
Trademark: Sumavel™ DosePro™
Established Name: sumatriptan (succinate)
Dosage Form: Injection
Route of Administration: Subcutaneous
Indication: Migraine

PAL: Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Summary and Critical Issues:

Summary

Sumatriptan succinate and sumatriptan are marketed by the innovator firm, GlaxoSmithKline, as Imitrex® under three approved applications, NDA 20-080 (Imitrex Injection, 4 mg/0.5 mL and 6 mg/0.5 mL), NDA 20-132 (Imitrex Tablets, 25 mg, 50 mg and 100 mg) and NDA 20-626 (Imitrex Nasal Spray, 5 mg and 20 mg). Imitrex Injection is marketed in two presentations, a prefilled cartridge containing either 4 mg/0.5 mL or 6 mg/0.5 mL sumatriptan (Imitrex StatDose®), and a 6 mg/0.5 mL vial. The approved route of administration is by subcutaneous injection. Zogenix has submitted a 505(b)(2) application that provides for marketing of sumatriptan injection, 6 mg/0.5 mL, in a prefilled needle-free injector. The proposed tradename for this drug/device combination is the Sumavel™ DosePro™.

The Sumavel™ DosePro™ (sumatriptan injection) drug delivery system (previously designated as the Intraject® system) was originally developed by Aradigm Corporation. After a pre-IND meeting between Aradigm and the Agency held on 28-Jun-2005, rights to the product were transferred to the current applicant. Zogenix submitted IND 71,275 on 29-Sep-2006.

During the IND phase, Zogenix sought Agency advice and concurrence on CMC-related issues via a CMC only pre-NDA meeting held on 21-May-2007 with representatives of ONDQA, OPS Microbiology Staff, and CDRH. Additionally, issues related to qualification of drug product degradants were discussed at the pre-NDA meeting between the clinical division and the firm on 11-Jun-2007. During the CMC-only meeting the Agency had reached agreements regarding supporting documentation for the bulk drug substance, the biocompatibility testing plan for device components, testing approaches for leachables and extractables, and submission of validation results for an alternate scale (b) (4) process (b) (4) in addition to

validation results for the full scale process. The firm also sought concurrence on filing strategies for scale-up and automation of (b) (4) device assembly operations. The draft comparability protocol submitted by the firm in the meeting briefing package, however, did not provide sufficient information to support agreement on this issue and the sponsor was advised that it would be a matter for review when the application was submitted.

Drug Substance

The active ingredient, sumatriptan succinate [[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]-N-methylmethanesulphonamide butanedioate (1:1)], is a well characterized small molecule with molecular formula C₁₈H₂₇N₃O₆S and molecular weight 413.40. The drug substance is freely soluble in water. The bulk drug substance will be supplied by (b) (4) and CMC information for the bulk drug substance is incorporated by cross-reference to DMF (b) (4). The DMF has been reviewed and found adequate. [M. Farahani, review dated 22-May-07.] The applicant’s proposed acceptance specification for sumatriptan succinate is based on the test methods and acceptance criteria given in the USP monograph for sumatriptan (base).

Drug Product

The Sumavel™ DosePro™ system is a pre-filled, disposable, single use, needle-free injector device designed subcutaneous delivery of 0.5 mL of a sterile aqueous solution containing sumatriptan succinate (b) (4) equivalent to 6 mg sumatriptan base).

The unit formulation for the drug product is shown in the applicant’s Table 3.2.P.1-1. (b) (4)

With the exception of the (b) (4), the composition of the solution is identical to the approved innovator product, Imitrex® Injection.

Table 3.2.P.1-1. Unit Formula for Intraject Sumatriptan

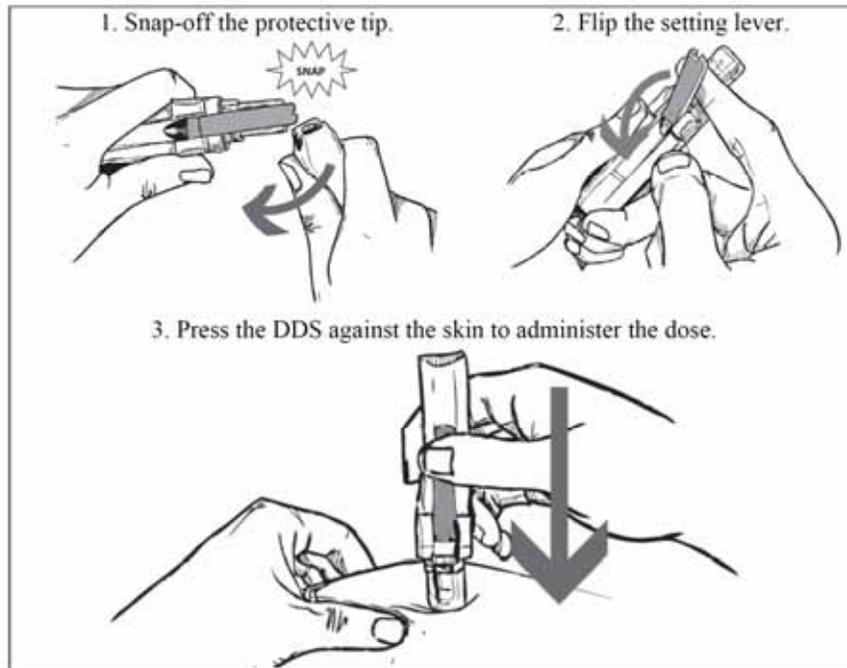
Component	Amount per unit (mg/0.5 mL fixed delivery volume ¹)	Function	Quality Standard
Sumatriptan succinate	(b) (4)	Active	In House Standard (Section 3.2.S.4)
Sodium Chloride	3.5	(b) (4)	USP
Water for Injection	(b) (4)		USP
Intraject® system			See Table 3.2.P.1-2

¹ Equivalent to 6.0 mg sumatriptan base

(b) (4)

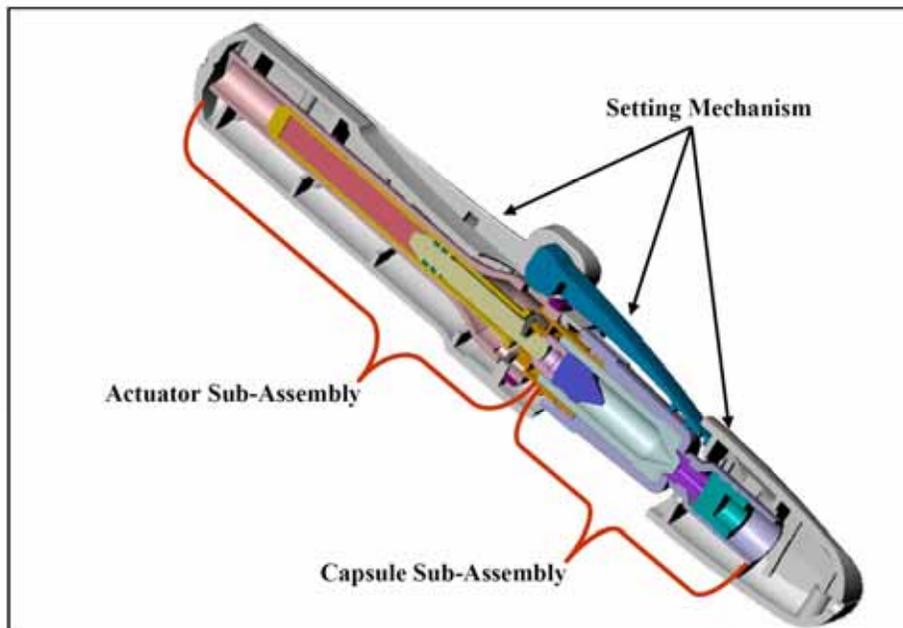
The DosePro™ system is designed for patient self-administration. The applicant states that the potential advantages over current injection systems include ease of administration, safe disposal without risk of needle injury or infection, and an alternative for patients with needle phobia. To use the DosePro™, the user snaps off a protective tip, flips a setting lever, and presses the device against the skin to administer the dose. [Figure 3.2.P.2.4-4]

Figure 3.2.P.2.4-4 Three Basic Steps for Using the Intraject Drug Delivery System

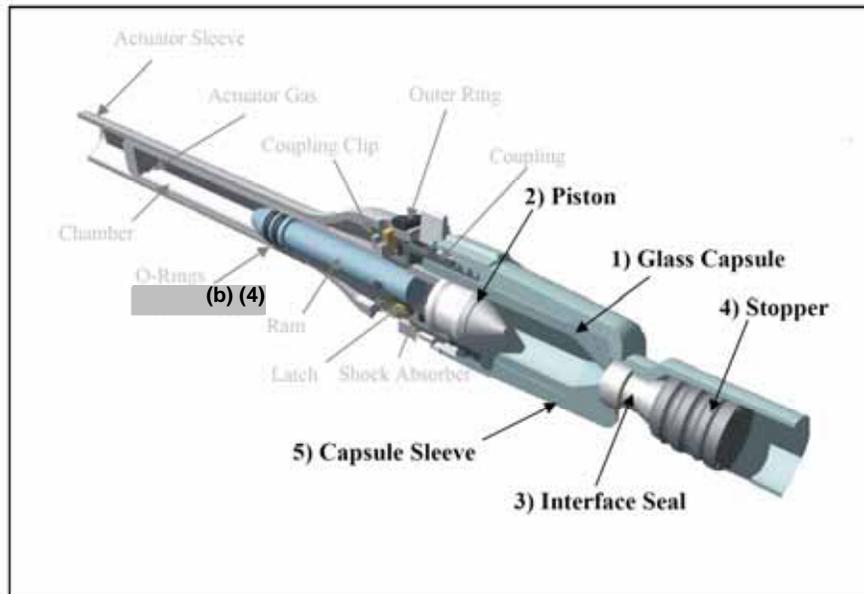


The device consists of a *capsule sub-assembly*, an *actuator sub-assembly*, and a *setting mechanism*. [Figure 3.2.P.2.4-1]

Figure 3.2.P.2.4-1 Intraject Sumatriptan DDS Sub-Assemblies



The *capsule sub-assembly* [Figure 3.2.P.2.4-2] is the primary container for the drug solution and contains the only product contact components.

Figure 3.2.P.2.4-2 Schematic of Capsule Sub-Assembly Components*

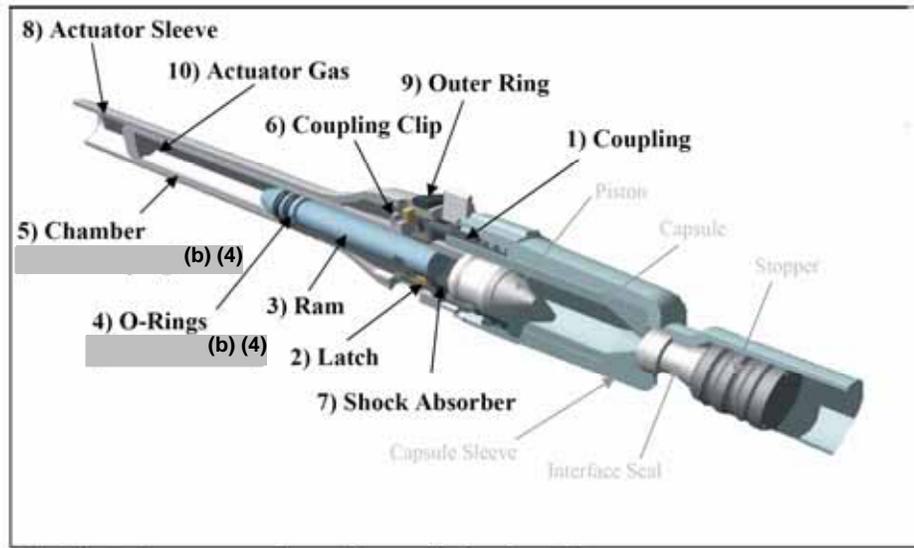
* For illustrative purposes the setting mechanism is not shown

The individual components of the capsule sub-assembly include:

- A glass capsule which stores the drug solution. During actuation, the solution is expelled through a small orifice at one end of the capsule to create a liquid jet.
- A piston that seals one end of the glass capsule, and expels the drug formulation when the device is actuated and controls delivered dose.
- An interface seal that allows sterile filling of the capsule sub-assembly under vacuum.
- A stopper which seals the other end of the glass capsule; the stopper is removed with the snap-off tip during preparation for injection.
- A capsule sleeve which protects the glass capsule and couples the capsule sub-assembly to the actuator sub-assembly.

The *actuator sub-assembly* [Figure 3.2.P.2.4-3] is powered by compressed nitrogen. When the device is actuated it expels the drug formulation and controls the delivered volume.

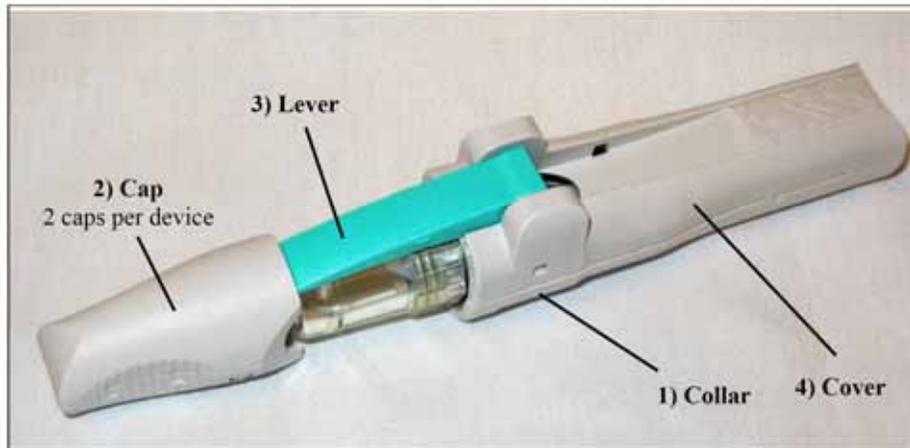
Figure 3.2.P.2.4-3 Schematic of Actuator Sub-Assembly Components*



* For illustrative purposes the setting mechanism is not shown

The actuator sub-assembly components include:

- A coupling to join the actuator sub-assembly to the capsule sub-assembly.
- A latch, which restrains the ram from moving until the time of injection.
- A ram that drives the piston down the glass capsule when the DDS is actuated, thus expelling the drug formulation through the drilled orifice.
- Two o-rings that seal between the ram and the chamber (b) (4) (b) (4)
- A chamber that stores the pressurized gas for expelling the drug formulation. (b) (4)
- A coupling clip to join the chamber to the coupling.
- A shock absorber that controls the initial rise of pressure in the drug formulation and eliminates the impact of bubbles that may be at the orifice at the time of actuation.
- An actuator sleeve that restrains the latch until the device is actuated.
- An outer ring to strengthen the actuator sleeve where the latch pushes against it.
- Pressurized actuator gas used to drive the ram when the device is actuated.

Figure 3.2.P.2.4-5 Intraject Drug Delivery System

The *setting mechanism* [Figure 3.2.P.2.4-5] consists of four functional parts:

- The two cap components enclose the snap-off portion of the capsule sleeve. The caps provide additional leverage to assist the user in removing the snap-off tip of the device, exposing the orifice to allow injection. The caps also lock the setting lever prior to use.
- The lever can only be operated when the snap-off tip is removed. When rotated and placed into the groove in the cover, the lever sets the actuator triggering mechanism and unlocks the actuator and capsule sub-assemblies.
- The collar and cover components form the handle of the DDS. The collar and cover support the actuator sub-assembly and the lever, and are held by the patient during use.
- A pin on the collar component drives into and sets the actuator triggering mechanism as the user rotates the lever into the cover.

Figure 3.2.P.2.3-1 provides a brief overview of the manufacture and filling of the Sumavel™ DosePro™ device. All manufacturing steps except assembly of the actuator sub-assemblies are performed by the drug product manufacturer, Patheon UK, Ltd; actuators are assembled by Bespak.

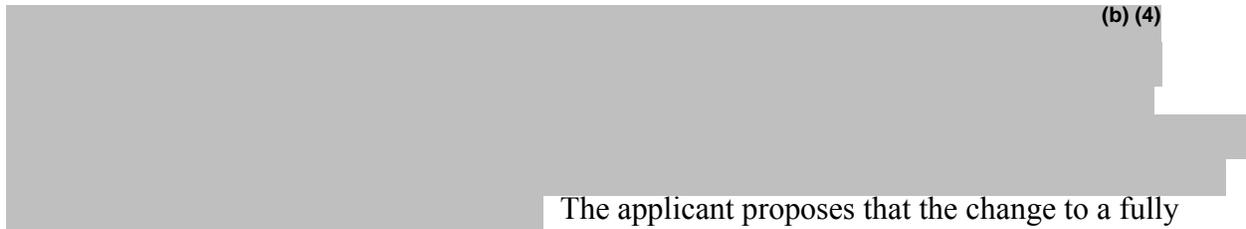
(b) (4)

(b) (4)

Figure 3.2.P.2.3-1 Intraject Sumatriptan Drug Product Manufacturing Overview



(b) (4)



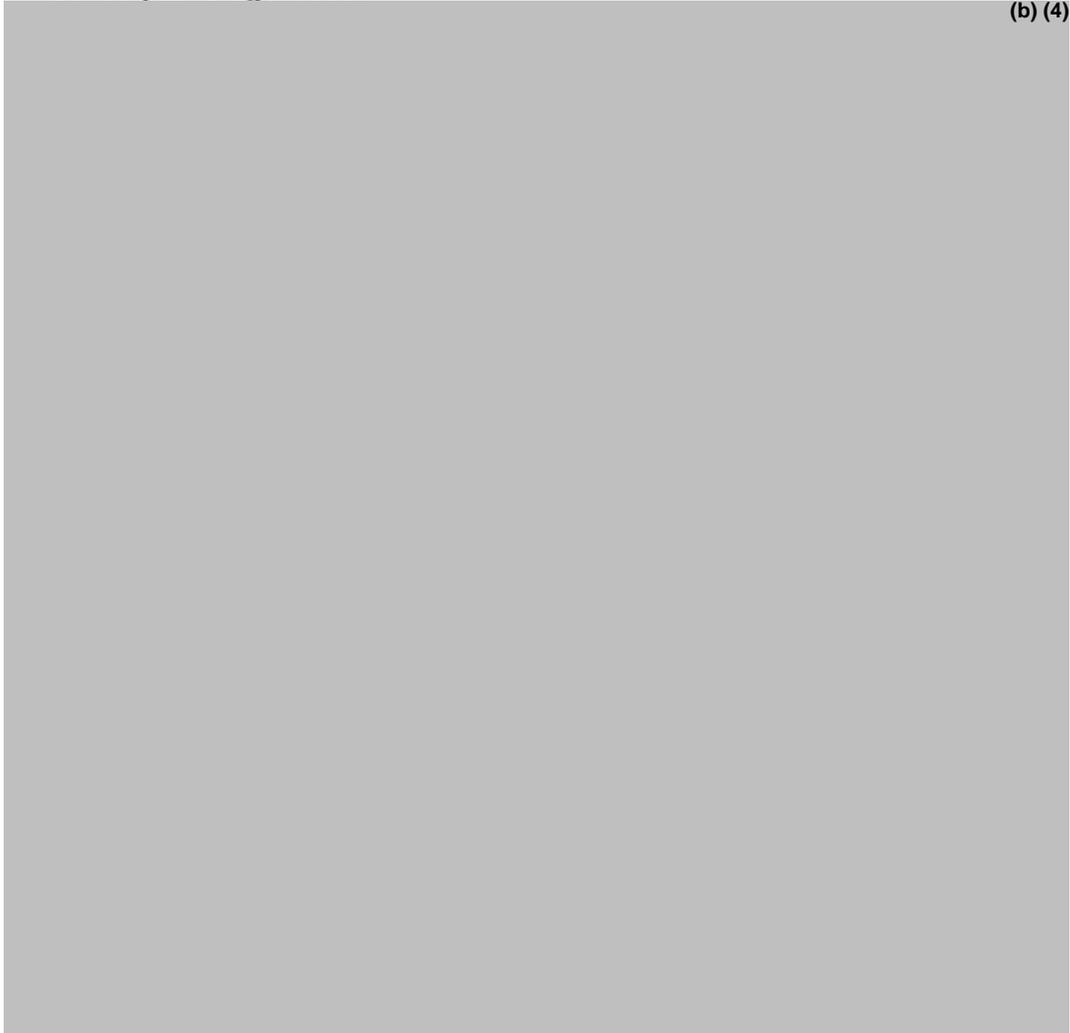
(b) (4)

The applicant proposes that the change to a fully automated process be evaluated during equipment qualification and submitted to the NDA as a minor amendment. The amendment would be submitted as part of the response to an approvable (AE), or tentative approval (TA) letter.

The proposed regulatory specification for the Sumavel™ DosePro™ is shown in the applicant's Table 2.3.P.5-1. The proposed product specification includes appropriate test parameters for a parenteral product to be delivered subcutaneously. The only device functionality test is a gravimetric test for dose accuracy. It is noted that the proposed specification includes limits for two degradants (Impurity 1 and Impurity 3) that exceed the ICH qualification, which is 0.5% for the 12 mg maximum daily dose. The applicant has provided stability data to demonstrate that comparable levels of both impurities are found in the approved product, Imitrex Injection. The proposed limits are also consistent with limits given in the USP monograph for Sumatriptan Nasal Spray. The applicant was advised by the clinical division that additional nonclinical studies would be required to qualify limits that exceed the ICH threshold. Pending completion of nonclinical studies, an interim specification of NMT (b) (4) is proposed for each impurity.

Table 2.3.P.5-1 Proposed Release and Stability Specifications of Intraject Sumatriptan Drug Product

(b) (4)



All release and stability tests involve straight-forward analytical procedures. A (b) (4) HPLC method is used for assay and determination of related substances. This method was developed specifically for the drug product. The method differs from the two methods used for assay/related substances and Sumatriptan Related Compound A, which are based on the UPS monographs for Sumatriptan and Sumatriptan Nasal Spray. USP HPLC methods for sumatriptan drug substance were used during development of the drug product and for early time points in the primary stability studies.

The NDA stability package includes data through 18 months under long-term storage conditions, 12 months data for intermediate storage conditions and 6 months of accelerated data for three primary stability batches. The primary stability batches were compounded at full commercial scale. (b) (4)



Critical issues for review

Drug Substance

No critical issues specific to the drug substance are identified. As noted previously, the applicant's acceptance specification for sumatriptan succinate is based on the USP Sumatriptan monograph. The monograph is referenced for all analytical procedures used during acceptance criteria. As the official USP reference standard is *Sumatriptan Succinate RS*, not sumatriptan base this should be considered acceptable.

Drug Product

The drug product is drug/device combination designed for subcutaneous injection. It contains an aqueous solution that is manufactured and filled into the device under (b) (4) conditions. The drug formulation is quantitatively identical to that of the marketed product, Imitrex (sumatriptan succinate) Injection, 6 mg/0.5 mL. The primary critical issues for the product are related to assurance of sterility and the design, control and performance of the delivery device design. The issue of sterility assurance will be addressed by the Microbiology reviewer. Evaluation of the device design, performance and manufacturing controls should be done in consultation with the CDRH review division possessing the required expertise. The following additional points will need to be considered during the review.

Manufacturing Process Automation: The original NDA submission provides for use of (b) (4) assembly and inspection processes. As discussed during the CMC pre-NDA meeting, the current processes can be used for commercial manufacture. The applicant has provided detailed information regarding the planned automation of the remaining processes and proposes submission of the change as a minor amendment to the NDA. The reviewer will need to evaluate whether additional documentation would be required to support any of the changes proposed, and whether submission of the changes should be classified as a minor or major amendment. It is recommended that the CDRH reviewer be consulted regarding this issue. As noted above, the Agency would not be able to approve the NDA during the current review cycle. It is expected that the manufacturing changes would be submitted as part of the firm's response to an Agency AE or TA letter. Classification of the any of the proposed changes as a major amendment would affect the review clock for the resubmission.

Regulatory Specification: As noted, the clinical division has required additional nonclinical studies to qualify two degradation products that are also observed in the approved product, Imitrex Injection. As the nonclinical studies are ongoing, evaluation of the drug product stability package and assignment of the expiration dating period will need be based on the interim specification.

Additional issues

Administrative: A claim for categorical exclusion from environmental assessment is included in Module 1 of the application.

Microbiology: The product is required to be sterile, thus a microbiology review is required. A microbiology consult was requested by the ONDQA Project Manager on 23-Jan-2008.

Delivery Device: An Inter-Center consult was sent to CDRH on 23-Jan-2008.

Establishment Evaluation: Drug substance and drug product manufacturing sites are listed within the application; however, the information is not provided with the Form 356h. This appears to be an oversight as the form indicates that the information is appended. Additionally, the applicant has not provided contact information or registration numbers for the drug product manufacturing sites. The EER will be submitted when the information is provided by the firm.

Labeling/Established Name: The product is labeled based on the content of the active moiety, sumatriptan, not the salt form. The applicant was advised to use the established name 'sumatriptan injection' in labeling prior to submission of the NDA. The firm has done this and there are no issues related to consistency between the established name and labeled potency. It is noted that the innovator product, Imitrex Injection, is labeled as 'sumatriptan succinate injection.' Correction of the innovator labeling is a separate issue that should be addressed in the future.

Comments for 74-Day Letter

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective. The drug substance is a well-characterized small molecule and the active formulation is relatively simple. The device design is novel and the manufacturing processes related to assembly of the device are somewhat complex. The device portion of the application will be consulted to CDRH and the OPS Microbiology Staff will be consulted regarding sterile process validation. Therefore, the submission does not appear to require a review by the Manufacturing Sciences Branch; assignment of a single reviewer is recommended.

Martha R. Heimann, Ph.D.
Pharmaceutical Assessment Lead

05-Feb-2008
Date

Ramesh Sood, Ph.D.
Branch Chief

05-Feb-2008
Date

ATTACHMENT 1

Manufacturing Sites for Sumatriptan Injection

Facility Information	Function
(b) (4)	
<p>Patheon UK, Limited Kingfisher Drive Covingham, Swindon Wiltshire, SN3-5BZ United Kingdom</p> <p>Registration No.: 9610802 Site Contact: Tel. No.:</p> <p>US Agent: Phone:</p>	<p>Drug product manufacture, release testing, labeling.</p> <p><i>Site contact information needed.</i></p>

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

/s/

Martha Heimann
2/5/2008 11:58:19 AM
CHEMIST

Ramesh- I revised the sections about the planned automation
(pp. 7 & 9) to clarify timing of
the amendment.

Ramesh Sood
2/6/2008 08:31:55 AM
CHEMIST