

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022569Orig1s000

CHEMISTRY REVIEW(S)



NDA 22-569

**Lazanda
Lazanda (fentanyl) Nasal Spray**

Archimedes Development Limited

**Julia C. Pinto, Ph.D.
Office of New Drug Quality Assessment, Division III**

Division of Anesthesia, Analgesia and Addiction Products

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Chemistry Review Data Sheet

Chemistry Review Sheet

1. NDA 22-569
2. REVIEW #: 2
3. REVIEW DATE: February 22, 2011
4. REVIEWER: Julia C. Pinto, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	28-Aug-2009
Amendment	04-Dec-2009
Amendment	17-Feb-2010
Amendment	01-April-2010
Filing letter	12-Nov-2009
IR letter ₁	08-Jan-2010
IR letter ₂	02-Feb-2010
IR letter ₃	08-March-2010
IR letter	07-April-2010
IND ^{(b) (4)} Meeting Minutes	18-Sept-06

- 1) Sent by Mathew Sullivan, Project Manager, via e-mail on 8th January 2010, to Archimedes
- 2) Sent by Mathew Sullivan, Project Manager, via e-mail on 24-Feb-2010 2010, to Archimedes
- 3) The 08-March-2010 letter requested microbiology related information.

6. SUBMISSIONS BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission NDA	09-30-2010
Amendment	11-19-2010
Amendment	11-29-2010
Amendment	12-10-2010
Amendment	02-21-2011
Amendment	02-25-2011

7. NAME AND ADDRESS OF APPLICANT:

Name: ARCHIMEDES DEVELOPMENT LIMITED
Address: Albert Einstein Centre
Nottingham Science and Technology Park
University Boulevard
Nottingham NG7 2TN, UK
Representative:



Chemistry Review Data Sheet

Ann C Tunstall (Herndon VA USA)
SciLucent, LLC
US Agent to Archimedes
Telephone: 703 435 0033 ext. 224

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Lazanda
b) Non-Proprietary Name: Fentanyl Nasal Spray
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S
-

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

8. Product Drug Code and Name:

- a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Fentanyl Nasal Spray
c) Code name/#(ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: Type 2
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(2)

10. PHARMACOLOGICAL CATEGORY:

Treatment of break through cancer pain in patients already receiving and are tolerant to opioid therapy

11. DOSAGE FORM: Nasal Spray

12. STRENGTH/POTENCY: 100mcg/spray and 400mcg/spray (in terms of fentanyl base)

13. ROUTE OF ADMINISTRATION: Intranasal

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

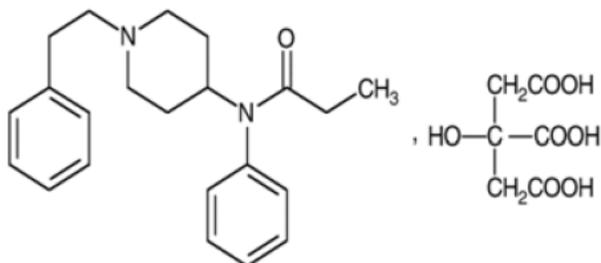
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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

Fentanyl Citrate



INN Name: Fentanyl Citrate

USAN name: Fentanyl Citrate

IUPAC name: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl] propanamide dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Other Chemical names:

N-(1-phenyl-4-piperidyl)propionanilide citrate

Propanamide, *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-Propanetricarboxylate

Molecular formula: $C_{22}H_{28}N_2O \cdot C_6H_8O_7$

Relative molecular weight 528.6 (citrate), 336.5 (base):

17. RELATED/SUPPORTED DOCUMENTS:

A. DMFs: See Review #1 (Sheldon Markofsky)

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code ¹	Status	DATE REVIEW COMPLETED	COMMENTS
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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")



Chemistry Review Data Sheet

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	70,854	Fentanyl Nasal Spray

18. Status

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Adequate	June 25, 2010	Office of Compliance
Pharm/Tox	Adequate	Rev #1	
Biopharm	Adequate	Rev #1	
LNC	NA		
Methods Validation	NA		
DMET/DDMAC			
EA	Categorical exclusion satisfactory	4-10- 2010	S. Markofsky

The Chemistry Review for NDA 22-569

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, was provided in the original NDA submission (Chem Rev 1, S. Markofsky). However, deficiencies were observed, in the device used to administer the drug product. Further, an adequate recommendation was pending from the office of compliance, for the Drug substance and drug product manufacturing sites. This resubmission addresses the deficiencies cited in the Agency's CR letter of June 30, 2010. The only changes made are to the container closure system and the development of patient instructions to use an activated carbon lined pouch that would be used to prevent exposure of fentanyl to the environment or caregivers. Further, during this review cycle, the Applicant requested a product name change from (b) (4) to Lazanda. The new name was approved by DMEPA. The data provided satisfactorily assures the identity, strength, purity, and quality of the drug product. The flaws observed in the spray device, during the first review cycle, have been adequately addressed. The addition of the carbon-lined pouch, as currently designed, retains all the fentanyl product in the vial. The extraction studies used to determine the ease of extraction of the fentanyl from the pouch, were facile experiments. They demonstrated that acetone can be used to extract 30% of the drug from the pouch. Therefore the pouch is not considered to be "addict-safe". That is, the pouch as it is designed, can prevent accidental exposure to the patients, caregivers and the environment in general. However, given the extreme methods that an addict will undertake to isolate the fentanyl, the pouch is not considered to be adequate protection against deliberate manipulation.

The drug substance, drug product formulation and product attributes remain the same as that submitted and reviewed in the original NDA submission. The Office of Compliance has issued an "Acceptable" overall recommendation for all facilities involved in production of the product

Therefore, from the CMC quality standpoint, the Applicant has adequately addressed the deficiencies sited in review #1 including providing a pouch as protection from accidental exposure to the environment. However, the burden of developing an "addict-proof" disposal system has not been met. Therefore while CMC recommends approval based on the quality of the drug product, assessment of the abuse potential of the pouch, is deferred to the clinical and CSS staff. If Clinical and/or CSS deems the pouch as it is currently designed to be a risk, then CMC recommends that the Applicant develop a different, more robust addict-proof disposal system.

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

No Post Approval commitments are required.

II. Summary of Chemistry Assessment

A. Description of Drug Substance and Drug Product:

The drug substance, Fentanyl Citrate, is a narcotic analgesic and a Schedule II controlled substance that binds to opioid receptors. The Chemistry, Manufacturing, and Control (CMC) information for Fentanyl Citrate was provided in DMF (b) (4) was reviewed and found to be adequate (see NDA Chem Rev #1, S. Markofsky).

The drug product, Lazanda, is a Fentanyl in a metered nasal spray (FNS). It is an aqueous solution containing 1.0 mg/ml or 4.0 mg/ml fentanyl base (present as citrate salt), equivalent to 1.57 mg/ml and 6.28 mg/ml fentanyl citrate, respectively. The solution components consist of the active substance, (b) (4) pectin (b) (4) (mannitol) (b) (4) phenylethyl alcohol (b) (4) propylparaben/ml). The pH of the solution is adjusted to the required range using hydrochloric acid or sodium hydroxide as necessary. The solution is intended for intranasal administration by delivery to the nasal mucosa via a multi-dose nasal spray pump. The drug product utilizes a pectin influenced nasal drug delivery system to modulate the delivery and absorption of fentanyl. This system allows the drug product to be delivered as a (b) (4) viscosity solution in a fine mist spray. On contact with calcium ions in the nasal mucosa, pectin forms a gel and fentanyl is systemically absorbed from this gel.

FNS is presented in a 5.3 ml capacity, USP Type I glass bottle sealed with a locking screw closure, a (b) (4) metered-dose nasal spray pump containing an integrated visual and audible spray-counter, and a mechanical end-of-use lock. The bottle has a U-shaped internal chamber to minimize fill volume. Each actuation of the pump will deliver (b) (4) of solution containing 100 µg or 400 µg fentanyl. When primed, the pump will deliver eight sprays before it locks. The commercial product will contain (b) (4) of FNS solution. Experimentally, the firm found an average of (b) (4) remains in the container after the final spray. This volume corresponds to (b) (4) of fentanyl base, depending upon the strength of the nasal spray. The recommended storage temperature is 25° C (77° F) (b) (4) and an expiry of 24 months.

During the first review cycle (by S. Markofsky) several deficiencies were noted in the nasal spray container/closure system.

Briefly these issues were that the

1. container closure system could not prevent accidental exposure to the fentanyl solution by patients, caregivers, and house hold contacts.
2. container closure system was inadequate to ensure an accurate accounting of the number of sprays.
3. method of disposing the used spray pump and the priming operation did not adequately protect household contacts from accidental exposure to fentanyl solution.

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Executive Summary Section

These deficiencies have been resolved in this resubmission without any changes made to the formulation or drug product characteristics.

B. Description of How the drug is intended to be used:

Lazanda is an opioid analgesic indicated only for the management of breakthrough cancer pain in patients who are already receiving and who are tolerant to regular opioid therapy. Each dose is administered as a single spray into one nostril or a single spray into each nostril (2 sprays). Each spray delivers 100 mcL of solution containing either 100 mcg or 400 mcg fentanyl base with the initial dose being 100 mcg.

C. Basis for Approvability Recommendation

The Office of Compliance has issued an "Acceptable" overall recommendation for all facilities. From the CMC quality standpoint, the Applicant has adequately addressed the deficiencies cited in review #1 including providing a pouch as protection from accidental exposure to the environment. The flaws observed in the spray device, during the first review cycle, have been adequately addressed. However, the burden of developing an "addict-proof" disposal system has not been met. Therefore while CMC recommends approval based on the quality of the drug product, assessment of the abuse potential of the pouch, is deferred to the clinical and CSS staff. If Clinical and/or CSS deems the pouch as it is currently designed to be a risk, then CMC recommends that the Applicant develop a different, more robust addict-proof disposal system .

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

Chemistry Reviewer: Julia Pinto, Ph.D.

Pharmaceutical Assessment Leader: Danae Christodoulou, Ph.D.

Project Manager: Matthew Sullivan

Acting Branch Chief: Prasad Peri, Ph.D.

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/s/

JULIA C PINTO
03/03/2011

PRASAD PERI
03/03/2011
I concur

Memo to File

DATE: June 26, 2010

TO: NDA 22-569, Fentanyl Nasal Spray

FROM: Sheldon Markofsky, Ph.D., Chemistry Reviewer

RE: Satisfactory Establishment Inspection Report

The Establishment Inspection Report, dated 6-25-10, indicates that the cGMP status for all of the relevant manufacturing and testing facilities are **Acceptable** for NDA 22-569.

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA remains approvable at this time, pending adequate responses to our Discipline Review Letter and Microbiology and CMC Information Request Letters from the applicant.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22569

ORIG-1

ARCHIMEDES
DEVELOPMENT
LTD

[REDACTED] (b) (4) (fentanyl nasal spray)

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/s/

SHELDON B MARKOFSKY
06/25/2010

(b) (4)

(fentanyl) Nasal Spray

NDA 22-569

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

Applicant: Archimedes Development Limited, Albert Einstein Centre
Nottingham Science and Technology Park, University Boulevard
Nottingham NG7 2TN, UK

Indication: Management of breakthrough cancer pain in patients who are already receiving and who are tolerant to regular opioid therapy.

Presentation: FNS will be provided in a 5.3 mL USP type I glass bottle containing (b) (4) fentanyl solution sealed with a locking screw closure, a metered-dose nasal spray pump containing a visible and audible spray counter, and a mechanical end-of-use lock. The bottle has a U-shaped internal chamber (b) (4)

The container will also be provided with a child resistant outer container. A photograph of the FNS pump, bottle and child resistant container is shown below. The clear glass bottle comes attached with a spray pump which delivers 100 µL each per actuation. The nasal spray delivers fentanyl base 100 mcg/spray and 400 mcg/spray. The glass bottle is packaged in a child resistant plastic bottle which is packaged in a white and yellow carton. Each bottle delivers eight (8) sprays after priming after which the dose counter locks the device.



EER Status: Pending Inspection of Drug Product manufacturing facility (b) (4) as of 25-May-2010.

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Not likely to pursue since the methods are standard.
Microbiology: Unacceptable
Pharmacology/Toxicology – Acceptable

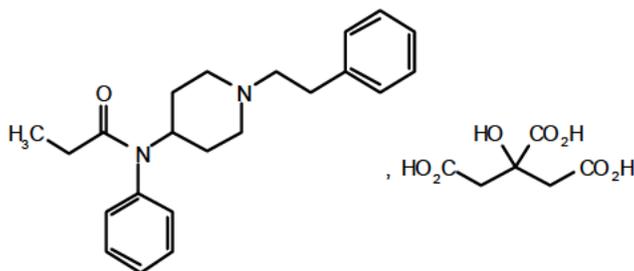
Original Submission: 28-Aug-2009

Post-Approval CMC Commitments:
None

Drug Substance:

The drug substance, a narcotic analgesic and a Schedule II controlled substance that binds to opioid receptors in the body, is referred to as Fentanyl Citrate. It is approximately 80 times more potent than morphine. The drug substance is a white crystalline powder that is soluble in methanol, sparingly soluble in chloroform and dissolves in water to the extent of about 1 gram in 40 ml. It is highly lipophilic,

The Chemistry, Manufacturing, and Control (CMC) information for Fentanyl Citrate that was provided in DMF (b) (4) held by (b) (4) and was reviewed and found to be adequate to support the NDA.



The drug substance specifications include Description, Appearance of Solution, ID (IR and UV), Assay, Related Substances, (b) (4), (b) (4), (b) (4), Ordinary Impurities, and Related Substances.

Conclusion: The drug substance is satisfactory.

Drug Product:

PecFent is a Fentanyl Nasal Spray (FNS). PecFent's metered spray is an aqueous solution containing 1.0 mg/ml or 4.0 mg/ml fentanyl base (present as citrate salt), equivalent to 1.57 mg/ml and 6.28 mg/ml fentanyl citrate, respectively. The solution comprises the active substance, (b) (4), (b) (4) (mannitol) and (b) (4) phenylethyl alcohol/ ml (b) (4) propylparaben/ml). The pH of the solution is adjusted to the required range using hydrochloric acid or sodium hydroxide as necessary. The solution is intended for use as an intranasal spray, which is delivered to the nasal mucosa via a multi-dose nasal spray pump. The drug product utilizes a pectin influenced nasal drug delivery system to modulate the delivery and absorption of fentanyl. This system allows the drug product to be delivered as a (b) (4) viscosity solution in a fine mist spray. On contact with calcium ions in the nasal mucosa, pectin forms a gel; and fentanyl is absorbed from this gel.

FNS is presented in a 5.3 ml capacity, USP Type I glass bottle sealed with a locking screw closure, a (b) (4) metered-dose nasal spray pump containing an integrated visual and audible spray-counter, and a mechanical end-of-use lock. The bottle (b) (4) has a U-shaped internal chamber (b) (4). Each actuation of the pump will deliver (b) (4) of solution containing 100 µg or 400 µg fentanyl. When primed, the pump will deliver eight sprays before it locks. The commercial product will contain (b) (4) of FNS solution. Experimentally, the firm found an average of (b) (4) remains in the container after the final spray. This volume corresponds to (b) (4) of fentanyl base, depending upon the strength of the nasal spray.

There are outstanding issues, mainly having to do with the container/closure system, that need to be resolved before the drug product can be approved for marketing:

- The pump assemblies could be unscrewed from the glass containers, without the use of tools, leading to open bottles of dangerous fentanyl solution. This is considered a serious safety issue due to the likely absorption of fentanyl from the skin as well.
- Flaws in the pump assembly could lead to incorrect priming of the pump, dose counting errors, and undesirable contact of the fentanyl solution with the patient's hands.
- There is still a significant amount of residual fentanyl solution (b) (4) remaining after use.

The specifications for the finished product include testing for Appearance, Identification, Assay, Related Substances, Spray Content Uniformity, Pump Delivery, pH, Osmolality, and Microbial Quality, Viscosity, Particulate Matter, Droplet Size Distribution, Spray Pattern, Weight Loss, and Leachables. Net Fill is monitored in process.

The drug product is manufactured at (b) (4) Quality Control operations are performed at (b) (4), Archimedes Development Center, Nottingham, UK, and (b) (4). The proposed commercial batch size is (b) (4).

The recommended storage temperature is 25° C (77° F) (b) (4). An expiry of 24 months is proposed and is found acceptable.

Outstanding issues:

- Adequate responses to our Discipline Review Letter: Microbiology and CMC Information Request Letters from the applicant. [It is especially important that the container closure system be modified to prevent accidental spills or contact with the drug product (fentanyl) solution.]
- An acceptable cGMP status for the relevant manufacturing and testing facilities.

Conclusion: The drug product is **not** recommended for approval.

Additional Items:

All associated 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 **NOT** recommended for approval.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22569

ORIG-1

ARCHIMEDES
DEVELOPMENT
LTD

[REDACTED] (b) (4) (fentanyl nasal spray)

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/s/

PRASAD PERI
05/25/2010

Memo to File

DATE: May 5, 2010

TO: NDA 22-569, Fentanyl Nasal Spray

FROM: Sheldon Markofsky, Ph.D., Chemistry Reviewer

RE: Structure Product Labeling (SPL)

Due to recent revisions in the recommended terminology to be used for the SPL drug labeling data elements, the SPL labeling comments, suggested on p.99 of Chemistry Review #1 for NDA 22-569, should not be conveyed to the applicant (Archimedes Development Limited). According to our SPL expert consultant, Lonnie Smith, Archimedes was apparently aware of the revisions to the terminology and correctly filled out the SPL drug labeling data elements table.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22569

ORIG-1

ARCHIMEDES
DEVELOPMENT
LTD

[REDACTED] (b) (4) (fentanyl nasal spray)

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/s/

SHELDON B MARKOFFSKY
05/05/2010

NDA 22-569

PecFent (fentanyl) nasal spray

Archimedes Development Limited

Sheldon Markofsky, Ph.D.
Division of Anesthesia and Rheumatology Drug
Products (HFD-170)

and

Office of New Drug Quality Assessment I
Branch II

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III. List Of Deficiencies To Be Communicated (Discipline Review Letter).....	101

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA #: 22-569
2. REVIEW #: 1
3. REVIEW DATE: 15-April-2010
4. REVIEWER: Sheldon Markofsky, Ph.D.
5. PREVIOUS DOCUMENTS:

Original	28-Aug-2009
Amendment	04-Dec-2009
Amendment	17-Feb-2010
Amendment	01-April-2010
Filing letter	12-Nov-2009
IR letter ¹	08-Jan-2010
IR letter ²	02-Feb-2010
IR letter ³	08-March-2010
IR letter	07-April-2010
 (b) (4) Meeting Minutes	18-Sept-06

- 1) Sent by Mathew Sullivan, Project Manager, via e-mail on 8th January 2010, to Archimedes
- 2) Sent by Mathew Sullivan, Project Manager, via e-mail on 24-Feb-2010 2010, to Archimedes
- 3) The 08-March-2010 letter requested microbiology related information.

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	28-Aug-2009
Amendment ¹	04-Dec-2009
Amendment ²	17-Feb-2010
Amendment ³	01-April-2010

- 1) The 12-04-09 amendment provided an updated list of manufacturing and testing facilities.
- 2) The 2-17-10 amendment updates the CMC information in the NDA and provides responses to our 1-8-10 Information Requests.
- 3) The 4-1-10 amendment updates the CMC information in the NDA and provides responses to our 2-24-10 Information Requests

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: ARCHIMEDES DEVELOPMENT LIMITED
Albert Einstein Centre
Address: Nottingham Science and Technology Park
University Boulevard
Nottingham NG7 2TN, UK

Representative: Ann C Tunstall (Herndon VA USA)
SciLucent, LLC
US Agent to Archimedes
Telephone: 703 435 0033 ext. 224

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: PecFent
- b) Non-Proprietary Name: Fentanyl nasal spray
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Management of breakthrough cancer pain in patients who are already receiving and who are tolerant to regular opioid therapy

11. DOSAGE FORM: Nasal Spray

12. STRENGTHS/POTENCY: 100 mcg/spray and 400 mcg/spray
(The potency is in terms of fentanyl base.)

13. ROUTE OF ADMINISTRATION: Intranasal

14. Rx/OTC DISPENSED: Rx OTC

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

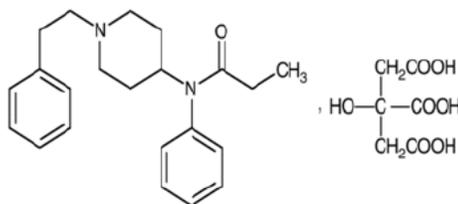
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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

Fentanyl Citrate

**Chemical Names**

INN Name: Fentanyl Citrate

USAN name: Fentanyl Citrate

IUPAC name: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl] propanamide dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate

Other Chemical names:

N-(1-phenyl-4-piperidyl)propionanilide citratePropanamide, *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-propanetricarboxylateMolecular formula: $C_{22}H_{28}N_2O \cdot C_6H_8O_7$

Relative molecular weight 528.6 (citrate), 336.5 (base):

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	3-29-10	
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	5-12-03 and 11-18-09	
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate information is in the NDA		

Chemistry Review Data Sheet

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	70,854	Fentanyl Citrate Nasal Spray

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Methods Validation	Validation by FDA labs. is not needed.		
EA	Satisfactory	4-15-10	S. Markofsky
Microbiology	Pending ¹		S. Fong

1) Microbiological information was requested from the applicant, but a full response has not yet been received.

Chemistry Assessment Section

The Chemistry Review for NDA 22-569

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA is approvable at this time, pending:

- Adequate responses to our Discipline Review Letter and Microbiology and CMC Information Request Letters from the applicant
- An acceptable cGMP status for the relevant manufacturing and testing facilities

[Labeling will be finalized at a later date as part of the review team's labeling negotiation.]

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)

Drug Substance:

Fentanyl Citrate

The drug substance, a narcotic analgesic and a Schedule II controlled substance that binds to opioid receptors in the body, is referred to as Fentanyl Citrate.

The drug substance is a white crystalline powder that is soluble in methanol, sparingly soluble in chloroform and dissolves in water to the extent of about 1 gram in 40 ml. The pKa of fentanyl citrate is 8.4.

The Chemistry, Manufacturing, and Control (CMC) information for Fentanyl Citrate that was provided in DMF (b) (4) was reviewed and found to be **adequate** to support the NDA.

Chemistry Assessment Section

Drug Product:

PecFent is a Fentanyl Nasal Spray (FNS). PecFent's metered spray is an aqueous solution containing 1.0 mg/ml or 4.0 mg/ml fentanyl base (present as citrate salt), equivalent to 1.57 mg/ml and 6.28 mg/ml fentanyl citrate, respectively. The solution comprises the active substance, (b) (4) pectin, (b) (4) (mannitol) (b) (4) phenylethyl alcohol/ ml and (b) (4) propylparaben/ml). The pH of the solution is adjusted to the required range using hydrochloric acid or sodium hydroxide as necessary. The solution is intended for use as an intranasal spray, which is delivered to the nasal mucosa via a multi-dose nasal spray pump. The drug product utilizes a pectin influenced nasal drug delivery system to modulate the delivery and absorption of fentanyl. This system allows the drug product to be delivered as a (b) (4) viscosity solution in a fine mist spray. On contact with calcium ions in the nasal mucosa, pectin forms a gel; and fentanyl is absorbed from this gel.

FNS is presented in a 5.3 ml capacity, USP Type I glass bottle sealed with a locking screw closure, a (b) (4) metered-dose nasal spray pump containing an integrated visual and audible spray-counter, and a mechanical end-of-use lock. The bottle (b) (4) has a U-shaped internal chamber (b) (4). Each actuation of the pump will deliver (b) (4) of solution containing 100 µg or 400 µg fentanyl. When primed, the pump will deliver eight sprays before it locks. The commercial product will contain (b) (4) of FNS solution. Experimentally, the firm found an average of (b) (4) remains in the container after the final spray. This volume corresponds to (b) (4) of fentanyl base, depending upon the strength of the nasal spray.

There are outstanding issues, mainly having to do with the container/closure system, that need to be resolved before the drug product can be approved for marketing:

- The pump assemblies could be unscrewed from the glass containers, without the use of tools, leading to open bottles of dangerous fentanyl solution.
- Flaws in the pump assembly could lead to incorrect priming of the pump, dose counting errors, and undesirable contact of the fentanyl solution with the patient's hands.

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

PecFent is an opioid analgesic indicated only for the management of breakthrough cancer pain in patients who are already receiving and who are tolerant to regular opioid therapy (b) (4). The dose of the drug

Chemistry Assessment Section

product is a single spray into one nostril or a single spray into each nostril (2 sprays). Each spray of PecFent delivers 100 mcL of solution containing either 100 mcg or 400 mcg fentanyl base. The initial dose of *PecFent* is 100 mcg. Subsequently, the patients are instructed to individually titrate to an effective dose that provides adequate analgesia; and the patients are also instructed to wait at least (b) (4) before using *PecFent* to treat another episode of breakthrough cancer pain.

PecFent is presented in a 5.3 ml capacity, USP Type I glass bottle sealed with a locking screw closure, a (b) (4) metered-dose nasal spray pump containing an integrated visual and audible spray-counter, and mechanical end-of-use lock. The recommended storage temperature is 25° C (77° F) (b) (4). An expiry of 24 months is **proposed** and is **acceptable**.

C. Basis for Approvability or Not-Approval Recommendation

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA is approvable at this time, pending:

- Adequate responses to our Discipline Review Letter and Microbiology and CMC Information Request Letters from the applicant. [It is especially important that the container closure system be modified to prevent accidental spills or contact with the drug product (fentanyl) solution.]
- An acceptable cGMP status for the relevant manufacturing and testing facilities.

[Labeling will be finalized at a later date as part of the review team's labeling negotiation.]

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

N/A

B. Endorsement Block

N/A

C. CC Block

N/A

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22569

ORIG-1

ARCHIMEDES
DEVELOPMENT
LTD

[REDACTED] (b) (4) (fentanyl nasal spray)

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

/s/

SHELDON B MARKOFFSKY
04/23/2010

PRASAD PERI
04/23/2010
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

OND Division:	Anesthesia, Analgesia and Rheumatology	
NDA:	22-569	
Applicant:	Archimedes Development LTD.	
Stamp date:	August 30, 2009	
PDUFA Date:	June 30, 2010	
Trademark:	PecFec®, NasalFent	
Established Name:	Fentanyl citrate nasal spray	
Dosage Form:	Nasal spray 1mg/ml and 4mg/ml; each actuation delivers 100mcg/ml and 400mcg/ml	
Route of Administration:	Nasal	
Indication:	Management of breakthrough pain in cancer patients	
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.	
	YES	NO
ONDQA Fileability:	<u>√</u>	_____
Comments for 74-Day Letter:	<u>√</u>	_____

Summary, Critical Issues and Comments

A. Summary

The application is filed as a 505(b)(2), non-priority NDA with 10-month review clock. The referenced approved product is ACTIQ® (fentanyl citrate) Oral Transmucosal Lozenge, NDA 20-747. The application is supported by IND 70,854 and a Drug Master File for fentanyl citrate (b)(4)

PecFent® nasal spray (abbreviated FNS) is an alternative formulation to the approved fentanyl products, ACTIQ® (lozenge) and FENTORA® (buccal tablets) for management of breakthrough cancer pain. These fentanyl products provide analgesia via rapid onset and individualized dose titration. FNS is an aqueous clear solution, available in two strengths, 1.0 mg/ml or 4.0 mg/ml fentanyl base (present as the citrate salt), which is equivalent to 1.57 mg/ml and 6.28 mg/ml fentanyl citrate, respectively. Each actuation of the nasal spray pump will deliver (b)(4) of solution containing 100 mcg or 400 mcg fentanyl. FNS is presented in a 5.3 ml capacity, USP Type I glass bottle, sealed with a locking screw closure, (b)(4) metered-dose nasal spray pump containing an integrated visual and audible spray counter and mechanical end-of-use lock. The bottle (b)(4) has a U-shaped internal chamber (b)(4). When primed, the pump will deliver eight sprays before it locks. The commercial product is filled with (b)(4) FNS solution.

B. Review, Comments and Recommendations

Drug Substance

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

Chemical names:

N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] propanamide, 2-hydroxy-1,2,3-propanetricarboxylate

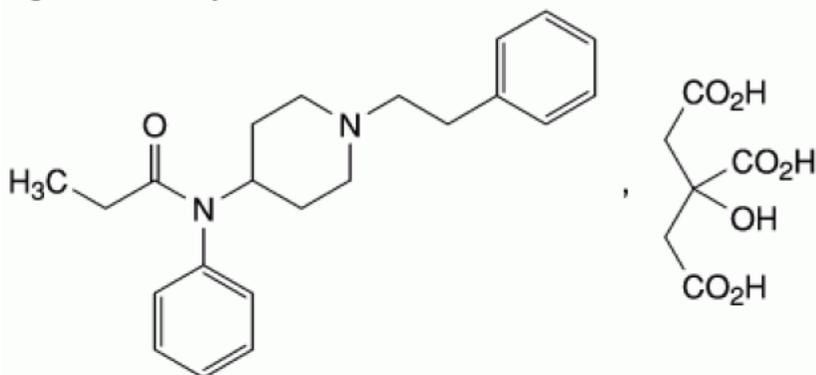
N-(1-Phenethyl-4-piperidyl) propionanilide citrate

Molecular formula: C₂₂H₂₈N₂O · C₆H₈O₇

Molecular Weight: 528.59 g/mol; Free base: 336.47 g/mol

CAS: 990-73-8

Figure 1. Fentanyl Citrate



The drug substance, fentanyl citrate, is supplied by (b)(4) Description of the manufacturing process and controls are referenced to the Drug Master File (DMF) (b)(4) Letter of Authorization (LoA) is included in the NDA. This DMF was reviewed previously. Proposed release (b)(4) and acceptance specifications by the applicant are included in the NDA. In early development (Phase 1, 2 and several pre-clinical studies) the drug substance was sourced from (b)(4) (b)(4) However, for Phase 3 clinical supplies and the proposed commercial product, fentanyl citrate is sourced from (b)(4)

Characterization:

Details of the drug substance characterization are referenced to the DMF. The physical properties of fentanyl citrate, e.g., solubility, morphic form, particle size distribution etc., should be assessed by the primary reviewer, for impact on manufacturability, quality and performance (e.g., bioavailability, stability) of the drug product. Since the drug product is formulated as aqueous solution, solid state properties are not expected to have an impact on the quality and performance (bioavailability) of the drug product.

Table 1.

Table 3.2.P.2.2-1: FNS Batch details illustrating change in API supply

Purpose	Date(s) of manufacture	Lot number(s) / fentanyl concentration (as base)	API supplier
Phase I single dose study (CP037/02)	April 2002	WFEN/002/F: 1 mg/mL	(b) (4)
Phase II (CP041/04)	Mar 2004	WFEN/008/F: 0.25 mg/mL	
	Feb/Mar 2004	WFEN/006/F: 1 mg/mL	
	Feb/Mar 2004	WFEN/007/F: 4 mg/mL	
	Jul 2005	WFEN/013/F: 0.25 mg/mL	
	Jul 2005	WFEN/014/F: 1 mg/mL	
	Jul 2005	WFEN/015/F: 4 mg/mL	
Rat toxicology, 90 day	Apr 2005	WFEN/009/F: Placebo	
	Apr 2005	WFEN/010/F: 4 mg/mL	
Dog toxicology, 9 month	Jul 2005	WFEN/011/F: Placebo	
	Aug 2005	WFEN/011A/F: Placebo	
	Jul 2005	WFEN/012/F: 4 mg/mL	
Rat toxicology, 6 month	Sep 2005	WFEN/016/F: Placebo	
	Sep 2005	WFEN/017/F: 4 mg/mL	
Phase I dose-proportionality (CP042/05)	Nov/Dec 2005	WFEN/018/F: 1 mg/mL	
	Dec 2005	WFEN/019/F: 4 mg/mL	

Potential Impurities and degradation products:

(b) (4)

13. The outer CR canister specifications should be assessed. The suitability of the CR canister to prevent overdose, misuse and diversion, and the child-resistant, senior-friendly functionality of the canister should be reviewed by appropriate disciplines.

14. The proposed expiration date is 24 months (b) (4)

D. **Comments for 74-day Letter:**

- Provide samples of the container/closure system assembled and disassembled, with labeled parts, for review.

Comments to be communicated after review by the primary reviewer:

End-of-use lock:

The proposed end-of-use lock has been implemented in the proposed commercial design. Clarify, if any nasal spray pumps of the proposed commercial design, which includes the end-of-use lock, have been tested in clinical trials, or in a patient in-use study.

Provide a description of the end-of-use lock, composition of components and engineering drawings; alternatively, you may request from your DMF supplier(s) to identify the information, specific to the end-of-use lock applied to your product, in their DMF(s), amendments.

Provide a justification for the selection of the mechanical end-of-use lock versus other physical and/or chemical methods, e.g., neutralization, to minimize residual fentanyl. We note that if the end-of-use lock is broken after the final actuation, (b) (4) of the residual volume can be recovered by repeatedly attempting to actuate the pump until no further drug product is delivered.

E. **Recommendation for fileability:** The NDA is fileable based on pre-NDA agreements sufficient number of NDA batches, and long term stability data for the drug substance and product. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

Recommendation for Team Review: The NDA is not recommended for team review.

Consults:

1. Toxicology

2. Microbiology (requested 10/13/09)

The primary reviewer, in conjunction with the project manager, should initiate the above consults.

Danae D. Christodoulou, Ph.D.
Pharmaceutical Assessment Lead

1/12/2010
Date

Prasad Peri, Ph.D.
Branch II Chief (acting), ONDQA

1/15/10
Date

NDA Number: 22-569

Supplement Number and Type:

Established/Proper Name:

(b) (4)

Applicant: Archimedes

Letter Date: 08/05/09

Stamp Date: 08/05/09

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		(M3)
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		Clarifications and communications with applicant/OC.
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 		X	Clarifications and communications with applicant/OC.

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	
-----	---	--	---	--

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Referenced to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Referenced to DMF (b) (4)
15.	Does the section contain controls for the DS?	X		Specifications included in the NDA
16.	Has stability data and analysis been provided for the drug substance?			Referenced to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		(Nasal spray, solution)

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	2	(b) (4)	(b) (4)	6/19/09	API
	3			4/14/09	(b) (4)
	3			4/15/09	Container/closure
	3			5/15/09	(b) (4)
(b) (4)	3	(b) (4)		4/9/09	Container/closure
(b) (4)	3	(b) (4)	(b) (4)	4/14/09	(b) (4)
				4/1/10	Container/closure

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?			Based on pre-NDA agreements and sufficient body of data
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		Describe filing issues here or on additional sheets
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	Describe potential review issues here or on additional sheets

{See appended electronic signature page}

Name of

PAL: Danae Christodoulou 10/12/09
 Division of Pre-Marketing Assessment I
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Name of

Branch Chief (acting): Prasad Peri
 Division of Pre-Marketing Assessment I
 Office of New Drug Quality Assessment

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	FENTANYL NASAL SPRAY

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

/s/

DANAE D CHRISTODOULOU
01/19/2010
Initial Quality Assessment

PRASAD PERI
01/19/2010
I concur

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

Application: NDA 22569/000	Action Goal:
Stamp Date:	District Goal: 01-MAY-2010
Regulatory:	
Applicant: ARCHIMEDES 585 GROVE ST STE 300 HERNDON, VA 20170	Brand Name: (b) (4) (fentanyl nasal spray) Estab. Name: Generic Name: FENTANYL NASAL SPRAY
Priority: 3	Product Number; Dosage Form; Ingredient; Strengths
Org. Code: 170	001; SOLUTION, SPRAY; FENTANYL CITRATE; 100UGM 002; SOLUTION, SPRAY; FENTANYL CITRATE; 400UGM
Application: NDA 22569/000	Action Goal:
Stamp Date: 31-AUG-2009	District Goal: 01-MAY-2010
Regulatory: 30-JUN-2010	

Applicant: ARCHIMEDES 585 GROVE ST STE 300 HERNDON, VA 20170	Brand Name: (b) (4) (fentanyl nasal spray) Estab. Name: Generic Name: FENTANYL NASAL SPRAY
Priority: 3	Product Number; Dosage Form; Ingredient; Strengths
Org. Code: 170	001; SOLUTION, SPRAY; FENTANYL CITRATE; 100UGM 002; SOLUTION, SPRAY; FENTANYL CITRATE; 400UGM

Application Comment: THIS IS A 505(B)(2) APPLICATION. THE REFERENCE LISTED DRUG IS ACTIQ (HOLDER IS CEPHALON) (on 28-SEP-2009 by D. HENRY () 301-796-4227)
CONTACT PERSON FOR THE APPLICATION IS ANN TUNSTALL, PHONE: 703-435-0033 EXT 224. FAX: 703-735-0440 (on 28-SEP-2009 by D. HENRY () 301-796-4227)

Contacts:	D. HENRY	Project Manager	301-796-4227
	S. MARKOFSKY	Review Chemist	301-796-1412
	D. CHRISTODOULOU	Team Leader	301-796-1342

Overall Recommendation: ACCEPTABLE on 25-JUN-2010 by A. INYARD ()

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

Establishment: **CFN:** ARCHIMEDES DEVELOPMENT LTD **FEI:** 3005103656

ARCHIMEDES DEVELOPMENT LTD
ALBERT EINSTEIN CTR UNIV.BLVD
NOTTINGHAM, , UNITED KINGDOM NG2TN

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: QC TESTING OF THE (b) (4) PECTIN) EXCIPIENT (on 22-OCT-2009 by D. CHRISTODOULOU () 301-796-1342)

Profile: CONTROL TESTING LABORATORY **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	22-OCT-2009				CHRISTODOULO
SUBMITTED TO DO	26-OCT-2009	10-Day Letter			STOCKM
DO RECOMMENDATION	30-OCT-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	04-NOV-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

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

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

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Estab. Comment: DRUG SUBSTANCE MANUFACTURER (on 06-OCT-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	22-OCT-2009				CHRISTODOULO
OC RECOMMENDATION	23-OCT-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS

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

Submission: CFN: (b) (4) FEI: (b) (4)

(b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Estab. Comment: MANUFACTURE, PACKAGING, QC RELEASE TESTING, AND TESTING OF THE DRUG PRODUCT. (on 06-OCT-2009 by D. HENRY () 301-796-4227)

Profile: AEROSOL DISPERSED MEDICATION 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	22-OCT-2009				CHRISTODOULO
SUBMITTED TO DO	23-OCT-2009	GMP Inspection			FERGUSONS
INSPECTION SCHEDULED	(b) (4)		(b) (4)		(b) (4)
ASSIGNED INSPECTION (b) (4)	13-MAY-2010	Product Specific			(b) (4)
DO RECOMMENDATION	24-JUN-2010			ACCEPTABLE	(b) (4)
PAI INSPECTIONAL COVERAGE WAS PROVIDED FOR THIS NDA APPLICATION. INSPECTION OCCURRED (b) (4); NAI; RECOMMEND APPROVAL.				INSPECTION	
DO RECOMMENDATION	25-JUN-2010			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

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

shment: CFN: FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Estab. Comment: PERFORM THE FOLLOWING QC TESTING OF THE DRUG PRODUCT: SPRAY FOR CONTENT UNIFORMITY, PUMP DELIVERY, DROPLET SIZE DISTRIBUTION, SPRAY PATTERN, AND PARTICULATES (on 06-OCT-2009 by D. HENRY () 301-796-4227)

Profile: CONTROL TESTING LABORATORY 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	22-OCT-2009				CHRISTODOULO
SUBMITTED TO DO	23-OCT-2009	10-Day Letter			FERGUSONS
DO RECOMMENDATION PREVIOUS INSPECTION NAI.	26-OCT-2009			ACCEPTABLE BASED ON FILE REVIEW	BSEEMAN
OC RECOMMENDATION	26-OCT-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

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

shment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: PERFORMS TESTING OF LEACHABLES. (b) (4) FOR DRUG PRODUCT (on 06-OCT-2009 by D. HENRY () 301-796-4227)

Profile: CONTROL TESTING LABORATORY 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	22-OCT-2009				CHRISTODOULO
SUBMITTED TO DO	23-OCT-2009	10-Day Letter			FERGUSONS
DO RECOMMENDATION	28-OCT-2009			ACCEPTABLE	(b) (4)
A CGMP AND PREAPPROVAL INSPECTION WAS CONDUCTED AT THIS FIRM ON (b) (4) THAT INSPECTION INCLUDED REVIEW OF TWO APPLICATIONS AND THE LABORATORY AND QUALITY SYSTEMS. NO FD483 WAS ISSUED AND NO VERBAL OBSERVATIONS WERE DISCUSSED. BASED UPON THAT INSPECTION AND THE FIRM'S INSPECTION HISTORY (b) (4) RECOMMENDS THIS FIRM AS ACCEPTABLE.					
OC RECOMMENDATION	28-OCT-2009			ACCEPTABLE	FERGUSONS
DISTRICT RECOMMENDATION					